



HAL
open science

Hydrogels for dermal and transdermal drug delivery

Hélène Labie, Muriel Blanzat

► **To cite this version:**

Hélène Labie, Muriel Blanzat. Hydrogels for dermal and transdermal drug delivery. *Biomaterials Science*, 2023, 11 (12), pp.4073-4093. 10.1039/d2bm02070j . hal-04092558

HAL Id: hal-04092558

<https://hal.science/hal-04092558v1>

Submitted on 3 Oct 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

REVIEW

Hydrogels for dermal and transdermal drug delivery

H  l  ne Labie^a and Muriel Blanzat^{a,*}Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

A painless and non-invasive method to deliver drugs using dermal and transdermal administration routes is expanding for more than 30 years as it reduces the risk of drug overdoses that can be associated with oral administrations or injections. To understand the particularities of this drug delivery pathway, we will present a rapid review of the skin, including its structure and the parameters that influence drug diffusion into it, and then discuss the strategies that improve dermal drug delivery. Of the multitude of existing systems used for topical dermal and transdermal applications, this review will focus on the breakthroughs in drug delivery systems made of hydrogels. Specifically, we will firstly present the use of hydrogels as innovative drug delivery vehicles to carry the active ingredient and penetrate the skin barrier. We will discuss, the structure of hydrogels and the physicochemical parameters to master for improving drug delivery, as well as the drug encapsulation and release purposes from hydrogels. In the last part, we will review the use of hydrogels as pharmaceutical forms associated with other vehicles – as emulsions, lipid nanoparticles, vesicles, capsules and polymeric or inorganic nanoparticles - suitable for skin penetration enhancement and drug protection as well as side effects that may limit their use.

1. Introduction

Drug delivery is a trending topic in pharmaceutical research, as many potential drugs would be made more promising and more widely used with a suitable delivery system. The design of drug delivery systems (DDS) depends on different parameters such as the drug's physical and chemical properties and the site of action. Topical drug delivery refers to the local release of a drug through vaginal, nasal or ophthalmic mucosa or through the skin. This approach could lead to better drug bioavailability and a decrease of side effects¹. Topical drug delivery release can be also considered when other delivery paths have failed.

Dermal drug delivery consist in a local and external application of a formulation by spreading it directly on the skin. The skin is the organ of the body with the largest surface area, making dermal drug delivery a promising and widely studied field of research². Dermal drug delivery includes mainly local dermatological applications to treat skin diseases such as psoriasis, eczema or fungal infections, but more recently, it is also used to deliver drugs for systemic circulation. In the first case, we talk about dermal application, while in the second one we talk about transdermal delivery.

Dermal and transdermal drug delivery have many advantages

over other pathways, such as a good patient compliance and ease of self-administration. These topical drug delivery systems can be designed to obtain a good drug bioavailability, but also to improve physiological and pharmacological responses. The duration of the treatment and its kinetics can be tuned by modulation of the exposure time and controlled release of the active ingredients.

For dermal applications, side effects can be decreased, as the surface of application can be easily selected and modulated, thus minimizing the exposure risks to healthy tissues. These treatments also allow a good efficiency at lower dose due to local application. Moreover, drugs with short biological half-lives can be used³. In the case of transdermal application, side effects are also limited. Transdermal delivery decreases systemic toxicity and avoids both the hepatic first path metabolism and the incompatibilities of the formulation with gastric system¹.

However, the topical route for drug administration has drawbacks which need to be overcome during the formulation process. For example, the application directly on the skin can lead to local irritation or allergies induced by contact between the skin and the drug or its formulation. Depending on the physical and chemical parameters of the active ingredients, such as their size and hydrophilic/lipophilic balance, some compounds cannot easily penetrate the skin². These limitations can be increased by a poor skin adhesiveness, or by a low patient compliance with treatments². Finally, for transdermal applications only a low drug amount can reach the systemic circulation. Among pharmaceutical formulations suitable for dermal applications, such as creams, ointments,

^a Laboratoire des IMRCP, Universit   de Toulouse, CNRS UMR 5623, Universit   Toulouse III – Paul Sabatier, France. Email : muriel.blanzat@univ-tlse3.fr

† Footnotes relating to the title and/or authors should appear here.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

lotions or gels, this review will focus on hydrogels, as they have many advantages. They are not greasy and have the ability to maintain hydration of the skin by retaining the water on skin surface^{4,5}. They are also composed of few ingredients, which is a great benefit to limit skin irritation and contact allergy issues.

2. Challenges for dermal or transdermal drug delivery

2.1. The skin is an efficient barrier

The skin is the interface between the internal body and the external environment, making it a crucial physiological barrier to avoid body contamination with pathogens. The skin's complex structure, comprising a series of parallel layers penetrated by hair shafts and gland ducts, limits the loss of water, electrolytes and other components out of the body. The major skin layers are, from inside to outside, the hypodermis, the dermis and the epidermis (Figure 1).

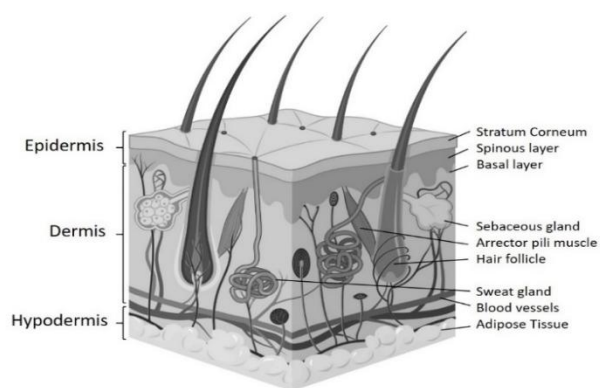


Figure 1. Structure of human skin. (Created with Biorender)

The hypodermis is a fatty layer of subcutaneous tissue where the lipids, as triglycerides, are stored for energy supply. While it plays major roles in thermoregulation and shock protection, the hypodermis is not involved in drug delivery. Indeed, for dermal delivery, only the upper layers—the dermis and the epidermis—are targeted; and for transdermal delivery, the molecules are absorbed by the blood circulation system before reaching the hypodermis.

The dermis is the intermediate layer of 1 to 2 mm thick that ensures firmness and elasticity of the skin. But its main role is nutritional, as it irrigates the epidermis thanks to its vascularization. The dermis is a connective tissue made of fibrous proteins (collagen and elastin), and fibronectin maintained by an aqueous matrix of glycosaminoglycans. Blood and lymphatic vessels, nerve endings, hair follicles, sebaceous glands and sweat glands are embedded within the dermis (Figure 1).

The upper layer is the epidermis, which is separated from the dermis by the dermo-epidermal junction that nutrients and waste have to cross (as the epidermis does not contain blood vessels). The epidermis is 50 to 100 μm thick and plays the role of barrier of the skin. It is made of 80% keratinocytes, but also contains melanocytes (responsible for skin color), Merkel cells

(responsible for sensory perception) and Langerhans cells (responsible for immune response). The epidermis is a stratified avascular layer made of five sublayers, which are from the inside to the outside the basal layer, the spinous layer, the granular layer, the clear layer and the horny layer also named stratum corneum (SC) (Figure 1). The epidermis without the SC is usually named the viable epidermis⁶. Each layer of the viable epidermis is defined by its position, its morphology and the differentiation state of its cells⁷.

The epidermis is a dynamic tissue. Basal keratinocytes, which reside in the deep basal layer, undergo keratinization. These keratinocytes differentiate and migrate to the surface within 3 to 4 weeks. Finally, they are flattened and compacted and turned into anucleated corneocytes cells to form the SC. The SC is about 10 μm thick, and is a unique biomembrane as it is the barrier for molecules permeation⁶. It is made of 15 to 20 layers of dead corneocytes^{8,9}. The structure of the SC is described as a brick-and-mortar arrangement (Figure 2)¹⁰, where the bricks are keratin-rich corneocytes embedded in the mortar made of intercellular lipid-rich matrix. The lipid domain's composition is predominant for drug delivery purposes and extensive research on its composition and structure have been performed¹¹. During epidermal differentiation, the lipid composition changes from a polar character to a neutral mixture¹². The major fractions in the SC are neutral lipids and ceramides (sphingolipids) and a small amount of polar lipids and non-polar material such as squalenes. Among the neutral lipids, both saturated and unsaturated fatty chains are found. Thus, many lipid species exist in the horny layer, differing both in type and chain length; this complex lipid mixture forms bilayered structures¹³.

The epidermis prevents water loss and also restrains the uptake of detrimental agents from the environment. However, the epidermis also hampers the penetration of drugs applied on the skin. Thus, to reach deeper skin areas and deliver drugs to the dermis or to the systemic circulation, specific pathways are identified. Two are transepidermal pathways and another is called the transappendageal route (Figure 2)¹⁴. Two mechanisms are described to deliver drugs through the epidermis. The drugs can be transported through corneocytes in the SC (trans- or intracellular route), or alternatively and more frequently, such drugs can diffuse through the interstices between the horny cells in the outer skin region (intercellular route) (Figure 2)^{15,16}.

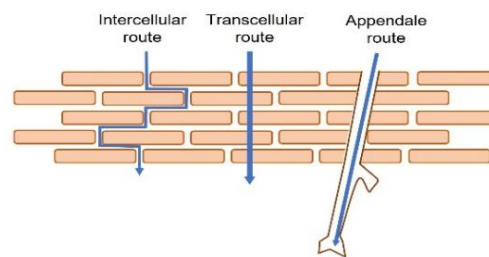


Figure 2. Pathways for drugs to cross the skin.¹⁷

The third pathway is the penetration through the hair follicles and gland cavities, as they open directly into the environment (Figure 2). It is called the transappendageal route or the shunt route. However it is less frequent, as this route only concerns a very restricted surface area of the skin^{6,18}.

The intercellular pathway is regarded as the main route of permeation for most compounds despite the relatively small surface area available^{15,19}. Because the transcellular or intracellular route involves the crossing of hydrophilic domains (in the corneocytes) and hydrophobic domains (intercorneocytes), it is highly defavorable for most of the active ingredients in a drug formulation²⁰. By contrast, the intercellular pathway is favorable to lipophilic and amphiphilic drugs through the mortar lipid-rich matrix. Thus, the physical and chemical parameters of the active ingredients play a major role in drug permeation. The active ingredient should be lipophilic enough to cross the SC and hydrophilic enough to diffuse in the aqueous domains of the viable epidermis²¹. The ingredient's size is correlated to the diffusion coefficient and must be small enough (< 500 Da) to favor passive penetration into the SC²². Furthermore, non-ionic drugs have better permeation features. Indeed, due to very narrow and specific characteristics that have to be reached to ensure permeation of a drug, most of the active ingredients do not cross spontaneously the skin. It is thus a real challenge to design formulations to overcome this issue. Many strategies are investigated to enhance drug permeation through the skin and will be discussed in this review. Among them are the use of permeation enhancers, vehicles and/or suitable pharmaceutical forms.

2.2. Pharmaceutical formulations : hydrophilic, hydrophobic or emulsion bases

Many semi-solid pharmaceutical formulations are suitable for topical applications such as creams, ointments, lotions or gels. They can be classified with respect to the physicochemical properties of the base: hydrophilic formulations (lotions and hydrogels), hydrophobic formulations (ointments and oleogels), or emulsions that are mixtures of a hydrophilic and a hydrophobic phase (creams, bigels and emulgels). Creams and ointments are semi-solid formulations with plastic behavior while gels exhibit viscoelastic behavior, thus inducing different rheological features¹. The selection of one of these forms can have an impact on the delivery of the active ingredient, the patient acceptability, and the efficiency of the treatment. To discriminate between pharmaceutical forms, the patient compliance plays a major role. It depends on the texture of the product including appearance, odor, extrudability, sensation upon contact of the product with the skin, spreadability, tackiness and oily residual effect^{23,24}.

Ointments, creams and lotions are colloidal forms that could induce stability issues. Other drawbacks often described for ointments and creams include stickiness, oiliness or difficulty in spreading the product. These forms can lead to irritation or allergic reactions, especially induced by the use of surfactants.

They can also exhibit poor skin permeability and poor absorption of high molecular weight compounds^{25,26}.

Usually, creams and lotions are considered less oily than occlusive formulations and thus are more appealing to the patient. Moreover, they are easily washable. However, they are more prone to evaporation, which lowers the hydration of the skin.

On the other hand, ointments form an occlusive barrier, which improves skin hydration and absorption by the dermal route. Their occlusive properties and their water-free formulation protect the skin from irritations due to hydrophilic molecules while avoiding the use of preservatives. In addition, the residence time of the formulation is increased compared to lotions and creams. However, they are less attractive to the patients, as they are greasier and more difficult to spread and wash off.

To bypass these difficulties, gels, and in particular hydrogels, are a popular alternative²⁷. They can be classified in two main categories, depending on the nature of their liquid phase. Organogels or oleogels are gels with an organic or oily liquid phase²⁸, while hydrogels are water liquid phase-based^{29,30}. More recently, other type of gels have been investigated for topical drug delivery purposes, including bigels, aerogels and emulgels³¹.

Organogels are made of an organic phase entrapped in a three-dimensional network. Different types of organogelators are identified, among them polymeric gelators (e.g., poly(ethylene glycol), polycarbonate, polyesters, and poly(alkylene))³², gemini gelators (e.g., N-lauroyl-L-lysine ethyl ester)³³, synthetic peptides (e.g. Boc-Ala(1)-Aib(2)-β-Ala(3)-OMe)³⁴, low molecular weight gelators (e.g., fatty acids and n-alkanes)³⁵ or 4-tertbutyl-1-aryl cyclohexanols derivatives³⁶. The organic phase can be made of an organic solvent, mineral or vegetal oil³⁷.

Hydrogel is a fluid, water-based phase in which small quantities of solid compounds are arranged in a three-dimensional structure creating a network³⁸. These materials are hydrophilic polymeric networks that are soluble but not dissolved in water. Higher amount of drugs can be dissolved in gels than in other pharmaceutical forms described above, and they allow an easy migration of the drug to the application site³¹.

Among the gel categories, hydrogels have many advantages for topical applications. They have the ability to maintain hydration of the skin by retaining the water which evaporates transepidermally, they are emollient and they facilitate the transportation of active ingredients^{4,5}. In addition, hydrogels contain few ingredients—a gelling agent in a solvent—which limits skin irritation and contact allergy issues. Furthermore, they also reduce production costs, are compatible with many excipients and are thixotropic, making them capable of liquefying when agitated and of resolidifying when allowed to stand. They are non-greasy, not shiny, non-staining, and easy to use thanks to good spreadability. Moreover, they can be designed to have a good consistency and be easily washable^{39,40}.

Hydrogels have been reported to reduce skin irritation by absorbing moisture from the surface of the skin⁴¹. Acceptability of hydrogel versus other pharmaceutical forms assessed by patients with atopic dermatitis was studied by Trookman et al.; the studies showed that the use of a hydrogel formulation containing desonide was easy to use, comfortable and soothing, disappeared quickly, and was not drying, greasy, or shiny on the skin⁴². For topical applications, hydrogels are mainly used for antiseptics, emollients, antifungal formulations, as well as in wound healing and skin protection. They are also used as drug delivery systems to transport drugs or as pharmaceutical forms.

Hydrogels have important swelling capabilities, as they can absorb important quantities of water (up to 90 times their weight), which is then entrapped in the polymeric network³⁰. Among the polymers used to prepare hydrogels, many different structures can be found such as hydroxypropylmethylcellulose (HPMC), carbopols, or sodium alginate, they are described as gelling agents^{26,43}.

The polymers used can be differentiated as either synthetic or natural. Natural polymers are composed of biopolymers⁴⁴. Among the natural polymers, polysaccharides such as chitosan, alginate or hyaluronic acid or proteins such as gelatins are often used^{45,46}. The benefits described for this class of gels are their biodegradability and biocompatibility as well as their low toxicity, and in some instances their non-toxicity⁴⁷. Moreover, they have relatively common features with living tissues, making them more suitable for biomedical applications and well accepted by the body⁴⁸. The fact that biocompatible gels are already used in commercial medical applications and they are made of natural polymers are compelling factors to select this class of gels compared to synthetic gels⁴⁹.

However, nowadays most hydrogels available on the market are made from synthetic materials. This can be explained by their excellent physical, chemical and mechanical properties, which can be finely tuned. But the synthetic polymers have major drawbacks: they can be expensive to produce, are rarely renewable and can be non-environmental friendly⁵⁰. Among synthetic polymers, poly(ethylene glycol) (PEG) and poly(vinyl alcohol) (PVA) are widely used^{45,46}.

In this publication, we explore the new breakthroughs in drug delivery systems (DDS) made of hydrogels for topical dermal and transdermal applications, focusing on innovative drug delivery purposes and strategies used to penetrate the skin barrier. In this context, hydrogels can be used directly as vehicles to carry the active ingredients to the skin, but they can also be used as pharmaceutical forms associated with other vehicles suitable for skin penetration enhancement, drug protection and side effect limitations.

3. Hydrogels as drug carriers

As a result of their structure, a 3D network in a large amount of water, hydrogels have a high porosity that allows the encapsulation and the controlled release of drugs. These features can be modulated by controlling the crosslinking degree of the gels and the chemical moieties on the polymeric

chains⁵¹. Many studies prove the potential of hydrogels for dermal or transdermal drug delivery. Indeed, an advantage is that hydrogels can also protect the active ingredient and allow sustainable drug release⁵². Thus, their versatility can allow the release of proteins and peptides with a short half life³. Sustainable release is a tool to modulate the delivery rate using responsive materials⁵². This can be achieved using polymers sensitive to pH, temperature or by addition of biomolecules. The sustainable release can also be achieved by modulating the rate of diffusion in the gel matrix and by increasing the contact time of the active ingredient with the skin. Another parameter that needs to be controlled to master the DDS is the interaction between the polymer used as gel matrix and the drug. These interactions have an impact on both the drug encapsulation and their release⁵³.

3.1. Structure of hydrogels

Hydrogels are crosslinked to ensure physical stability of the 3D network. When the hydrogels are made of physical reversible crosslinks, they are named physical gels. These physical crosslinks can be made of entangled polymer chains, or by Van der Waals interactions or hydrogen bonds^{38,54}. Alternatively, covalent chemical bonds that form crosslinks between polymer chains lead to so-called chemical or permanent gels^{38,55}. Hydrogels can be prepared by different methods and with different precursors to adjust their properties such as porosity, mechanical strength and degradability^{45,56}.

In an original study, the matrix is made of polymers assembled in nanovectors. Thus, micelles made of modified PEG in aqueous solutions of α -cyclodextrins (CD) induce the formation of a micellar supramolecular hydrogel through the formation of host-guest inclusion (Figure 3). Diclofenac encapsulation in this formulation showed a significant increase of skin retention on the surface of the rabbit cornea compared to simple micellar solutions, thereby improving bioavailability in vivo⁵⁷.

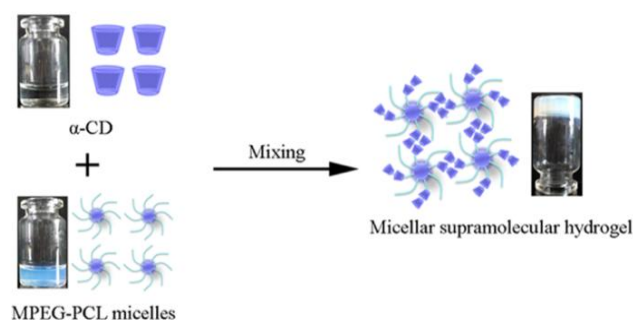


Figure 3. Formation of hydrogels using α -cyclodextrins (CD) and host-guest inclusion as crosslinkers. Reprinted with permission from Zhang Z, He Z, Liang R, Ma Y, Huang W, Jiang R, Shi S, Chen H, Li X. *Biomacromolecules*. 2016 Mar 14;17(3):798-807. doi: 10.1021/acs.biomac.5b01526. Epub 2016 Feb 12. PMID: 26830342. Copyright 2016 American Chemical Society⁵⁷.

3.2. Physicochemical parameters to master hydrogels for topical drug delivery purposes

Patient compliance and clinic efficiency are compulsory to ensure an effective treatment. For this purpose, certain criteria have to be fulfilled to optimize hydrogels formulations.

3.2.1. Spreadability. Gelled formulations are classified as semi-solid bases and have the property to cling to surface for an extended time before being washed off or removed⁵⁸. Topical therapeutic efficiency depends on the patient's action of spreading the formulation into a homogeneous layer, thus ensuring that a standardized dose of drug is administered. Optimized consistency helps to ensure that the correct dose is applied. Non-homogenous spreading can induce a too-low dosage in some areas of the application site. Conversely, the application of too high amount of drug in other areas could lead to a local overdose that induce potential side effects—especially if the drug is potent, e.g., active at low concentrations. Spreadability is related to the contact angle between the formulation and its substrate and is a measure of lubricity, which is directly related to the coefficient of friction⁵⁸. An experimental method developed by Barry and Grace evaluated the spreading of a formulation between two parallel plates at shear rates that mimic the application of a formulation on the skin²³. Experimental studies have shown that viscosity and degree of penetration of the formulation are linked by a logarithmic regression. Furthermore, a linear regression has been proven between permeation and spreadability⁵⁹.

3.2.2. Rheology. Rheological properties of gels lead to a better understanding of deformation and flowing capabilities under the effect of external forces. Targeting good rheological properties consists of designing the appropriated gels, e.g., a gel flowing easily out of their containers, easy to spread and with an appropriate texture⁶⁰. It is necessary to investigate changes induced by the different forces that the formulation will undergo during its fabrication and use and their effects on the formulation's stability over time. In order to know the rheological behavior of the formulations, measures of shear stress, strain and viscosity can be performed. Moreover, to obtain information on viscous and elastic behavior as well as microstructure of the topical gels, flow viscometry, oscillatory rheometry and transient measurements can be conducted. Rheological properties of gels can be modified by gel concentration, crosslinking degree and chemical modification of the network. As an example, hydrophobic moieties introduced in a gel chemical structure can induce new crosslinking points by hydrophobic interactions⁶¹.

A gel's rheological features have to be investigated in relation to the encapsulated drug, as the drug's presence in the gel network can induce modifications on gel properties. Gel nature, concentration and method of preparation can all influence drug release. In a study describing calcein release from different hydrogels such as hydroxyethyl cellulose (HEC) and Carbopol⁶², the authors have demonstrated that the nature of the gel was decisive, and had a greater effect on gel properties, than the gelling agent concentrations. Indeed, Carbopol have elastic solid behaviour, while HEC and

HEC/Carbopol gels exhibit viscoelastic properties. Calcein diffusion out of the Carbopol-based gel is faster. The same effect was observed for hydrophobic drug release from the same gel systems.

For topical formulations, the consistency of the samples is an important feature, due to the fact that it must be applied to the skin in thin layers. For this reason, it is preferable to formulate plastics samples because of their low resistance to flow when they are applied under high shear conditions. Conversely, at rest – under the stress caused by gravity – the flow is zero. Thus, plasticity is a desirable characteristic of the consistency of topical formulations^{63,43}.

3.2.3. Nature of the polymer chains. As discussed in the paragraph above, the nature of the polymer chains can have an important effect on a gel's rheological properties. However, among other parameters such as the interaction of the gel with the skin, and the solubility of the drug into the gel network, the nature of the gel also has an influence on the active penetration. Thus, Luppi et al. studied the influence of crosslinkers of chitosan hydrogels loaded with a hydrophilic drug model (propranolol hydrochloride). By modifying the polymer chemical and physical structure to add hydrophobic moieties, an amphiphilic chitosan gel matrix is obtained. The use of amphiphilic polymer to design the hydrogel structure has shown a promising capacity to enhance the active ingredient penetration through the biological membranes⁶⁴. This phenomenon is explained by the increased adhesion of the gel to the SC, promoting the solubilization of the active ingredient in the skin and increasing its speed of penetration. In this investigation, the interaction between the gel and the SC is attributed 1) to the addition of hydrophobic acylchain moieties on the chitosan chains, which gives it an amphiphilic character and 2) to its ability to partially dissolve in the upper part of the SC. Furthermore, it has been proven that these new systems are more efficient for shorter chains, such as hydrogels made from lauric and myristic acids compared to hydrogels made with longer chains such as palmitic and stearic groups. This can be explained by the longer acylchain moieties inducing a significant decrease of drug solubility.⁶¹

3.2.4. Occlusivity. It is of great interest for topical formulations to maintain skin moisture in the stratum corneum (SC). Occlusivity is the capability of a formulation to maintain or promote water loss in the SC. This parameter is determined in vivo by measuring the transepidermal water loss (TEWL) of the skin. The occlusive effect of a formulation depends on skin characteristics such as lipid content and prevailing environmental conditions.

In a randomized investigation of 20 participants with mild-to-moderate atopic dermatitis, it was reported that the water-based hydrogel vehicle improved skin hydration at baseline compared with moisturizing lotion and did not further impair epidermal barrier function⁶⁵. Spada et al. compared a lotion and a gel formulation containing 0.1% of mometasone furoate. The two pharmaceutical forms were proven to be bioequivalent, but the hydrogel formulation provided better

moisturisation⁶⁶. Application of the hydrogel resulted in a significant decrease of 43% in TEWL after 2h, which remained significant (29%) after 24 h. Skin hydration was also significant after 24 h, at 38% above baseline. Due to the similarity of this mometasone furoate hydrogel with a desonide hydrogel, improvement of patient adherence to the hydrogel application regimen based on previous preference studies with a desonide hydrogel was expected^{42,67,68,69}.

Occlusivity depends on formulation type, size and quantity of particles. It has a significant effect on drug release and permeation, as in occlusive condition (complete hydration of the SC) the skin is hydrated and the drug permeation is modified⁷⁰. Indeed, the hydrophilic/hydrophobic balance of the skin is modified, and depending on the drug characteristics, it can lower or increase diffusion resistance⁷⁰. Furthermore, occlusivity can have a direct effect on the pathology. Increasing water content in the skin reduces symptoms of eczema and improves skin appearance^{71,72}. Thus, occlusivity of gel/drug systems has to be considered in the assessment of treatment efficiency.

3.3. Drug encapsulation and release from hydrogels

To design appropriate topical drug delivery systems using hydrogels as vehicles, the nature of the active ingredient plays a major role. An ideal drug can be defined with optimal characteristics for a spontaneous penetration through the skin. The drug has to exhibit specific physical and chemical features such as a low molecular weight (< 500 Da), good lipophilic balance ($\log P_o/w \cong 1-3$) and a low fusion point. Due to these specific conditions needed for optimal passive diffusion through the skin, many active ingredients cannot spontaneously penetrate by dermal or transdermal pathways. However, this limitation can be bypassed. The design of the hydrogel systems has to consider the characteristics of the drug to ensure a good encapsulation and an optimum release.

3.3.1. Release mechanisms: diffusion, swelling, competitive chemical interactions. The release mechanism is another parameter to master in order to control the administration of the active ingredient. While gels can be used as vehicles, they can also behave as reservoirs where the drug is entrapped. Several models are described in the literature to predict drug delivery mechanisms from hydrogels over time. These models account for the rate-determining step. They can be classified in three categories: controlled by diffusion, controlled by swelling or controlled by chemical interactions⁷³.

Diffusion is governed by the drug movement through the gel network or by gel erosion. The classical pore size of hydrogels is a comprise between a few nanometers and 100 nm⁷⁴, which is larger than most of the low molecular weight organic molecules used as active ingredients. Thus, their release by simple diffusion out of the gel 3D matrix is not delayed. Many times, however, higher molecular weight molecules such as peptides or proteins with an important hydrodynamic radius could exhibit a sustainable release from the gel porous structure where they are encapsulated. These characteristics

allow loading and release of a drug with a kinetic correlated to its diffusion coefficient through the skin.

The controlled release of active ingredients from hydrogels can also be triggered by swelling of the gel as a response to an external stimulus such as change in pH, temperature or presence of a biomolecule⁷⁵. This can be a reversible reaction, inducing a temporary increase of the pores size of the 3D structure that leads to drug release. This mechanism of delivery can be used to target tissues affected by a disease if they have specific characteristics.

The use of pH-sensitive hydrogels capable of loading hydrophobic drugs have the potential to treat different skin conditions. A pH imbalance is one of the main causes leading to skin inflammation and acne. In normal conditions, the skin surface has a pH ranging from 5 to 6. Changes in the skin pH can potentially compromise the barrier function of the stratum corneum⁷⁵. Kwon et al. described a new type of hydrogel made of hyaluronic acid and cellulose to deliver an antimicrobial therapeutic agent for acne growth inhibition (isoliquiritigenin)⁷⁶. This type of hydrogel presented pH-responsive properties and was able to maximize the cargo release at around pH 7. The formation of acne presents the peak of activity at this pH. The drug was able to permeate the skin barrier via the follicular pathway due to the hydrogel-assisted swelling of the skin⁷⁶.

Another study showed the transdermal transport of diclofenac, an anti-inflammatory drug, over 24 h from a solid hydrogel. The delivery was greater than any other known diclofenac formulation⁷⁷. The temperature-dependent sustained release of diclofenac is made possible through the entrapment of temperature-responsive nanogels within the solid hydrogel structure⁵.

Other mechanisms can be induced by a chemical reaction in the gel matrix. The addition of a biomolecule in the site of action can trigger a non-reversible degradation of the gel matrix or of its pendant chains⁷⁸. The addition of a molecule can induce the release of drugs by competitive reaction or by modification of the drug/matrix interactions. Thus, under hyperglycemic conditions, phenylboronic acid units within the polymeric matrix reversibly form glucose–boronate complexes that—owing to their increased negative charge—induce the swelling of the polymeric matrix and weaken the electrostatic interactions between the negatively charged insulin and polymers, promoting the rapid release of insulin. However, for this application, single removable transdermal patches bearing microneedles are necessary to cross the skin and reach glucose molecules⁷⁹.

The first mechanism of drug release by simple diffusion is often described for a localized, non-specific drug delivery, which is the case for most of the topical applications. Responsive hydrogels are widely studied and used for oral, injectable or subcutaneous applications^{30,73}.

To summarize, topical drug delivery depends on physical and chemical properties of the drug and its capacity to permeate the skin. The parameters described above have to be mastered to ensure good design of the formulations. It leads to adapted treatment with good skin permeation, easy-to-use

formulations and body acceptability by avoiding side effects with adapted pH. Thus, well-designed hydrogels have optimal mechanical properties, such as easy removal of formulation from its container, large spreading on substrate, good rheological properties (viscosity, elasticity, thixotropy, flow) and other aspects such as bioadhesion, adapted release features and extended cutaneous absorption⁸⁰.

3.3.2. Strategies for hydrophobic drugs encapsulation.

Hydrogels are particularly suitable for the encapsulation and release of hydrophilic drugs because they are highly swollen in water and the drugs are well solubilized in the porous cavity of the gels. For hydrophobic drug release, the choice of the gel's characteristics is predominant to design suitable systems.

Because of this high compatibility with hydrophilic active ingredients, the delivery of hydrophobic drug is limited due to solubility issues [57]. However, recent new investigations showed that hydrophobic drugs can also be released from hydrogels. To perform release of hydrophobic drugs, solubility issues have to be overcome. For this purpose, different strategies have been developed: the chemical structure of the network can be modified using cyclodextrin moieties⁸¹, and hybrid structures such as bigels⁸² or amphiphilic polymers can be used to introduce hydrophobic zones in the gels where the solubilisation of the drug will be enhanced^{83,84}.

Thus, hydrogels including cyclodextrins in their structure can encapsulate hydrophobic compounds in the inner core of the CD. For example, non-covalent complexes involving drug and CD as a host-guest inclusion can be created, leading to formation of hydrogels of hydroxypropyl- β -cyclodextrin (HP- β -CD). These systems have proved their efficiency to encapsulate curcumin, an unstable and insoluble drug in water with a pharmacologic anti-cancerous activity. The inclusion of drugs in CDs modify their solubility, while increasing their stability and transdermal diffusivity, making these systems promising for treatment of melanoma cancer⁸⁵.

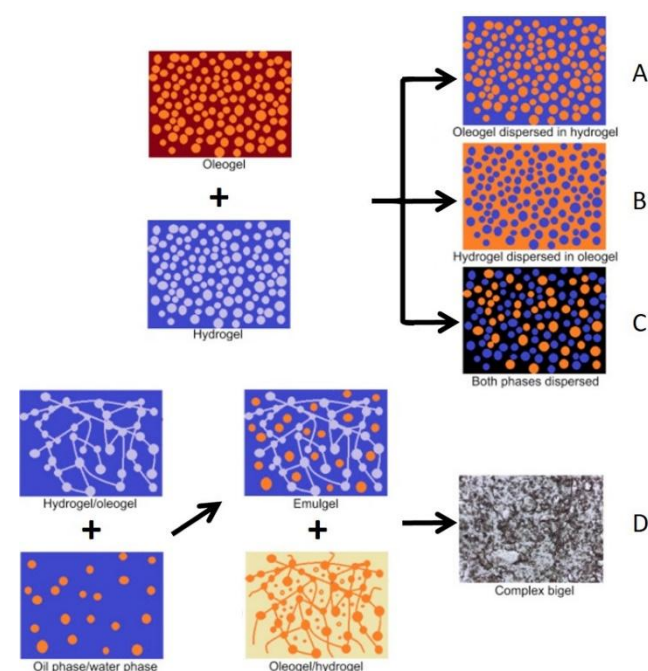
Finally, these systems have shown their capacity to sustain drug release over time, for example by including CDs in poly (hydroxyethylmethacrylate) gels in the formulation of contact lenses, which allows diclofenac release over 25 days⁸⁶. However, this strategy is limited to molecules of low molecular weight.

The second strategy to promote penetration of hydrophobic compounds delivered from hydrogels consists of using hybrid hydrogels called bigels (figure 4). Bigels are topical formulations obtained by combination of two immiscible gels, in particular hydrogels and oleogels, to induce a synergetic effect that favors SC hydration and permeation of drugs⁸⁷. Bigels are unique semisolid formulations made by combining the two gels at a high shear rate, which afterward exist as a uniform dispersion throughout. They can form different types of microscopic arrangements (Figure 4).

Bigels combine the properties of both systems—specifically cooling effect, SC hydration improvement, moisturizing effect, easily spreadable systems, emollient and water washability. Bigels can have pseudo plastic behavior and good mechanical properties to induce good spreading of the formulation⁵⁴.

They are prepared easily by mixing a hydrophilic system and a hydrophobic one at high shear rate; therefore, hydrophobic and hydrophilic compounds can be released. Their formulation without surfactants limits irritation issues⁸⁸.

Permeation mechanisms are similar to mechanisms described for hydrogels and oleogels: diffusion through the matrix and permeation through the SC is promoted by the use of oils of appropriate nature and/or by the presence of fatty acid chains. Zulfakar used these systems to release imiquimod, an immune response modifier currently used against skin diseases, by transdermal delivery⁵⁴. For this purpose, bigels made of a mixture of sodium alginate, fish oil and hydroxypropyl methylcellulose were studied and showed high cumulative permeation and drug flux compared to hydrogels alone. The



addition of fish oil in the formulations has a significant positive effect by increasing drug transdermal permeation⁵⁴.

Figure 4. Schematic diagram representing microscopic arrangements of different types of bigels. (a) Oleogel dispersed in hydrogel, (b) hydrogel dispersed in oleogel, (c) both phases are dispersed, and (d) Complex bigel. Adapted with reuse permission from⁸⁹. Licence number 5450680242516. Copyright 2018 Elsevier Ltd.

The moisturizing effect of bigels was investigated *in vivo* on 14 volunteers. The formulations prepared from Carbopol and oleogels made of almond oil and liquid paraffin are promising, as they kept the good sensory properties of hydrogels for topical applications while enhancing moisturizing effects⁸⁷. However, bigels can undergo a phase separation phenomenon and few aging studies have been performed so far to evaluate shelf-life of these products. Only a few formulations using bigels technology are commercially available in the market, among them is Bi-Gel Testosterone³¹.

Finally, the last strategy consists of using amphiphilic polymers in order to encapsulate the drug in hydrophobic domains⁹⁰. Amphiphilic gel microstructures consist mainly of clusters of tubules of gelator molecules that have aggregated upon cooling of the sol phase, forming a 3D network throughout the

continuous phase. These gels demonstrate thermoreversibility. Gelation temperature and viscosity increase with increasing gelator concentration, indicating a more robust gel network. At temperatures near the skin surface temperature, the gels softened considerably, which would allow topical application. Amphiphilic gels can be prepared by mixing a solid gelator like sorbitan monostearate or sorbitan monopalmitate with the liquid phase like liquid sorbitan esters or polysorbate, heating them at 60°C to form a clear isotropic sol phase and finally cooling the sol phase to form an opaque semisolid gel at room temperature⁹¹. However, this strategy is rarely investigated in the literature⁹².

3.4. Use of permeation enhancers

3.4.1. Use of chemical permeation enhancers. As described above, the physical and chemical properties of a drug do not always allow its dermal or transdermal release, even if they are associated with compatible hydrogel vectors. It can be necessary to use strategies to deliver drugs with appropriate quantities and kinetics. Thus, it is possible to use hydrogels in association with chemical permeation enhancers to promote drug diffusion into the skin by increasing the drug partitioning or its diffusivity into the SC⁹³. Several mechanisms are described in the literature: increase of the fluidity of SC lipid bilayer, increase of the SC hydration (occlusivity), increase of drug activity, intercellular lipid extraction and alteration of proteinaceous corneocytes^{94,16}. Chemical permeation enhancers are classified depending on their chemical structures. Among them are alcohols, fatty acids, amines, esters, amides, urea, hydrocarbons, surfactants, terpenes, sulfoxides and phospholipids.

Chemical permeation enhancers have been introduced in hydrogel formulations in several studies. In particular, chemical permeation enhancers such as ethanol, dimethyl sulfoxide, dimethyl isosorbide, isopropyl myristate and propylene glycol are compared by Martin et al. for the delivery of gabapentin, a drug used to relieve neuropathic pain⁹⁵. The cutaneous permeation of gabapentin is evaluated ex vivo on a human skin model. The research showed that ethanol and dimethyl sulfoxide promote the penetration of gabapentin incorporated in Carbopol gels. Another strategy consists of introducing permeation enhancing moieties directly on the polymer chains structures, especially on the pendant one⁶¹. Thus, Luppi has integrated hydrophobic acylchain moieties on chitosan, proving the improvement of hydrophilic model drug penetration⁶¹. It is important that the permeation enhancers do not decrease the drug solubility, as this could also decrease the drug bioavailability.

However, a recurring disadvantage is that the chemical permeation enhancers can induce cutaneous irritation. The mechanisms allowing a better drug permeation by disorganization of SC lipid bilayer or of corneocytes are the same mechanisms responsible for the cutaneous irritation⁹⁶. Moreover, chemical permeation enhancers are used to help the low molecular weight compounds to penetrate the skin but are less efficient on macromolecules.

3.4.2. Use of physical permeation enhancers. An alternative to chemical penetration promoters is the use of physical permeation enhancers. Needles are widely used as physical permeation enhancer to cross the skin, but they may be traumatic. This is why other techniques are developed, such as jet injections⁹⁷, dermabrasion⁹⁸, thermal ablation⁹⁹, laser¹⁰⁰, microneedles¹⁰¹, iontophoresis¹⁰², electroporation¹⁰³, ultrasound¹⁰⁴ or a combination of these methods. They are less traumatizing, more user-friendly and flexible and are able to produce bolus type as well as sustained drug delivery profiles. Among these techniques, some can be used for topical applications in combination with hydrogels and are described below.

Hydrogels are widely used to create patches containing microneedles to administer drugs by transdermal pathways. Donnelly et al. fabricated microneedle arrays from aqueous blends of poly (methylvinylether/maleic acid) and poly (ethylene glycol) via a micromoulding process using silicone moulds. The polymers formed a gel shaped as microneedles where the drug is encapsulated. The improvement of metformin HCL doses using transdermal microneedles in synthetic and pig skin in vitro models, and also in vivo in rats model, were investigated. They showed promising results, as the drug was detected in rat plasma, contrary to oral administration¹⁰⁵.

Gels are also considered the most suitable vehicles to use for the iontophoresis technique, as they can fuse with the iontophoretic delivery system and can follow the contours of the skin. Thus, the transdermal release of nalbuphine hydrochloride (NA) and nalbuphine pivalate (NAP) from hydrogel formulations of polyvinylpyrrolidone (PVP) and hydroxypropyl cellulose (HPC) have been studied. The use of iontophoresis allowed a significant increase of drug release compared to passive diffusion¹⁰⁶. Furthermore, insulin release from gels of poloxamer 407 assessed ex vivo and in vivo on rat models using iontophoresis have been studied in association with chemical permeation enhancers and alone. The use of iontophoresis coupled with addition of linoleic acid in the formulation lead to the release of insulin, inducing a decrease of glucose plasmatic concentration of 36 to 40 %¹⁰⁷. However, the use of iontophoretic devices is quite expensive, which limits their use for regular topical drug delivery applications⁷⁰. Low frequency ultrasounds (LFU) are used as a physical technique to promote drug permeation through the skin, as the areas exposed to LFU become locally heterogeneous and more easily allow drug entry. Hydrogels of different zeta potential (ZP) have been coupled to LFU to deliver calcein and doxorubicin (DOX). Heterogeneous areas where the drug permeation is facilitated are larger when hydrogels are present, inducing a higher skin permeation. Zeta potential has an impact on the DOX permeation, as it is a positively charged drug. Thus, the cationic hydrogel decreased the quantities of DOX collected from the viable epidermis by 2.8-fold. The anionic coupling medium, by contrast, increased the DOX accumulation in the SC by 4.4-fold as well as in the viable epidermis due to electrostatic repulsions (1.5-fold). Therefore,

LFU/hydrogel treatments increase localized transport regions and can target ionized drugs to specific skin layers, depending on the zeta potential of the hydrogel used¹⁰⁸.

4. Vectors-in-hydrogels systems

Despite the use of chemical or physical permeation promoters, some drugs require vectors or vehicles to be transported at the skin surface or in the dermis. These vehicles can be introduced in a gel matrix to associate the benefits from the vector and the hydrogel and promote dermal or transdermal delivery. The vectors can have several roles: they can protect the drugs from degradation, protect the skin from irritations induced by some drugs, or they can increase drug solubility and promote the permeation of the drug through the skin to increase its bioavailability. For drug delivery purposes, a vector can modify the release rate of an active ingredient or help it to penetrate the skin.

Most of the vectors used as drug carriers are colloidal nanostructures. These colloidal systems are mainly made of lipids and/or an organic/oil phase. This feature allows the encapsulation of hydrophobic active compounds, poorly soluble in water, which would otherwise exhibit solubility issues in hydrogels alone. In addition, the vectors-in-hydrogels systems can be used in combination with permeation enhancers.

Associations of vectors and hydrogels lead to hybrid materials with novel and original structural properties. Indeed, the physical and chemical properties obtained could not be reached with either forms alone. The crosslinked networks of the gel can protect the object's structure and extend the functionalities of the vectors and hydrogels. These systems have the capacity to modulate the drug pharmacokinetics by, for example, extending the residence time of these vectors at the application site¹⁰⁹.

A vector loaded with a drug can be released without structural modification from the hydrogel to further help pass through the skin^{110, 111}. In this case, vector integrity has to be preserved while it is in the gel, even if slight property modifications can be tolerated⁵². The vector can also modulate the kinetics of drug release, to obtain for example sustainable and controlled-release of the active ingredient. In this case, vector stability over time and in the gel structure is not compulsory, as the vehicle destabilization can tune the kinetics of release¹¹².

To master these systems, it is important to understand and control interactions between the vehicles and the hydrogels. The gels can be chosen accordingly to either retain or not retain the vectors in the 3D structures¹¹³.

4.1. Structure of hydrogels combined with vectors

Different hydrogels structures are described in the literature as some combination of hydrogels and nanovectors systems designed for drug delivery purposes. The first such structure consists of a suspension of vectors in a polymeric network

(Figure 5-A) while the second comprises the formation of hydrogels through the assembly of vectors (Figure 5-B). In the last one, a hybrid hydrogel is obtained, i.e., the hydrogel is composed of a polymer network in which the nanovectors are inserted as a crosslinking node (Figure 5-C)^{114,115}.

Figure 5. Structure of hydrogels combined with drug-vectors: A) the vector is in suspension in the porous structure, B) the hydrogel is made by an association of vectors, C) the network is made of polymer combined with vectors as crosslinking nodes.

Desai et al. used a system based on the third strategy. This study highlighted the encapsulation capacity of hydrophilic and hydrophobic active ingredients in a novel polyamidoamine (PAMAM) dendrimer hydrogel (DH). The dendrimer was modified to attach polymers (PEG) which formed the three-dimensional network. The hydrophilic active ingredients were entrapped in the network while the hydrophobic components were encapsulated in the dendrimer¹¹⁴.

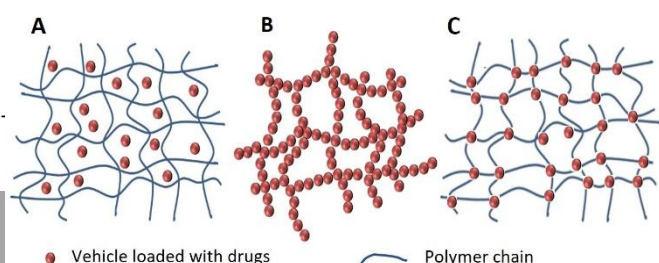
In the following section, promising vectors-in-hydrogels systems that are frequently studied for dermal or transdermal drug delivery purposes will be discussed. These nanocarriers can be of different types, such as vesicles, emulsions droplets, lipid nanoparticles or capsules.

4.2. Emulsions

4.2.1. Description of emulsion-based systems. Emulsions can be used as vehicles to transport drugs. Emulsions are colloidal dispersions comprising a dispersed and a continuous phase, one being aqueous and the other an oil phase. To stabilize the droplets of the dispersed phase, surfactants and sometimes co-surfactants are used with specific ratios. Emulsions can be classified depending on the size of their drops and their thermodynamic stability. Usually, emulsions that are kinetically stable but thermodynamically unstable are of two types: macroemulsions with a drop size between 1 and 100 μm and nanoemulsions with a drop size between 20 and 500 nm. Nanoemulsions are subject to stability issues and high amount of energy is necessary to prepare them, for example, using a high-pressure homogenization method. Finally, some emulsions are classified as microemulsions, and are thermodynamically stable with drop size between 10 and 100 nm.

The use of microemulsions has several advantages, as they do not induce significant cutaneous irritation and can be used to administer relatively large volumes of hydrophobic or hydrophilic drugs¹¹⁶. Furthermore, the solubilisation of the drugs favors transcutaneous penetration. In addition, the ingredients of the microemulsion can improve the diffusion through the SC by dissolving the lipids of the SC and providing penetration enhancement^{117,118,119,120}. Higher diffusion and absorption rates were observed from microemulsions compared to systems without solvent or surfactants¹²¹.

Microemulsions are stable, transparent, easy to prepare and are not very irritating because of the low amount of surfactant used. However, they have low viscosities, making their topical spreading difficult and restricting their pharmaceutical use. To overcome this issue, they can be associated with gels.



In fact, emulsions can in general be dispersed in gels¹²². When emulsions have a gelled continuous phase, they are named emulgels. These structures combine properties of emulsions and gels and act as dual control release systems¹²³. Emulgels are hydrogels when their continuous phase is aqueous and the droplets are oil-based.

The literature describes many emulgel systems and different droplet size ranges (micro or nanoemulsions) can be dispersed in gels. For example, nanoemulsions prepared by a high-pressure homogenisation technique can be used to prepare emulgels with carbomers. In this case, the viscosity is improved without losing stability, and the nanodroplets keep their size when dispersed in gels¹²⁴. Chen et al. prepared gels made of Xanthan or Carbopol to viscosify microemulsions without

stability loss or decrease of permeation rate¹²⁵. Many gelling agents have been used to prepare emulgels in association with microemulsions (or nanoemulsions) such as hydroxy propyl methyl cellulose (HPMC)¹²⁶, carrageenan¹²⁷ and carbomer.

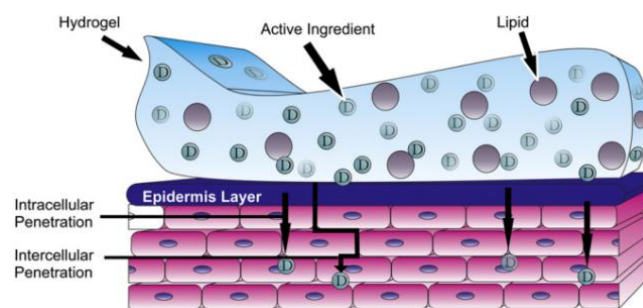
The use of emulsions-in-gels as drug delivery systems have several advantages. These formulations are thixotropic and non-greasy, particularly if the external phase is an aqueous, direct emulgel. They also exhibit good spreadability and are transparent, easily removable and non-staining. They also have good preservation and excellent emollient properties, which makes them appealing to patients.

The choice of the composition of the phases, such as gelling agent, oil or surfactant, impacts the stability and efficiency of

species inside the droplets (for direct emulsions). This latter has high surface area, which induces high area of contact between the drops and the skin, thus promoting good permeation capabilities.

Finally, emulsions can undergo the occlusive effect, and the oil and surfactant used can act as chemical permeation enhancers²¹. Emulgels can deliver both hydrophilic and/or hydrophobic drugs (Figure 6). Some drawbacks frequently described for emulgel systems include poor absorption of macromolecules and the entrapment of bubbles during their preparation³¹.

The team of Vora studied microemulsions in gels as a means of administering bifonazole, an antifungal drug¹²⁸. Hydroxy propyl methyl cellulose (HPMC) gels were used to disperse microemulsions containing bifonazole. Oleic acid was used as the dispersed phase, Tween 80 as surfactant, isopropyl alcohol as co-surfactant, and HPMC was dispersed in water as continuous phase (2% of HPMC is the optimal concentration to obtain a high viscosity). The pH of the formulation of 5.3 was



Hydrogel Material	NPs Material	Drug loaded	Biomedical Application	Conclusions	Reference
Carbopol 940	Microemulsion (oleic acid, Labrasol, Transcutol P, water)	Terbinafine	Antifungal	Increased retention in the skin and an enhanced antifungal activity	31
Carbopol 940	Microemulsion	Diclofenac	Anti-inflammatory	Easy spreadability, long shelf-life and reduce diffusion barrier of SC	31
HPMC	Microemulsion	Chlorphenesin	Antifungal	Gel with very stable viscosity. High drug release and antifungal activity	122
Carbopol 940	Microemulsion based on clove oil	Mefenamic acid	Anti-inflammatory	High skin penetration. Good anti-inflammatory analgesic agent	21,122
HPMC	Microemulsion (oleic acid, Tween 80, IPA, water)	Bifonazole	Anti-fungal	Improved viscosity, spreadability and cutaneous permeation	128

Table 1: Summary of microemulsion-hydrogel systems used for dermal or transdermal biomedical applications

the treatments. Ingredients can be chosen to deliver eco-friendly formulations.

Emulgels can be used in many applications, including to release analgesic, anti-inflammatory, antifungal or anti-acne drugs. Several commercial formulations are available such as Voltaren, Voveran, Voltarol, Biogel, White glow or Topicane³¹. Moreover, a drug encapsulated in the droplets of an emulsion can pass in the external gelled phase and be absorbed by the skin. The droplets are like reservoirs, allowing a slow and controlled release.

The external gelled phase can encapsulate small molecules and allow their diffusion through the skin. Due to its mucoadhesive property, contact with the skin is extended¹²². These systems allow high loading capacity of hydrophobic

close to the pH of the skin. The optimized formulation improved the properties in terms of viscosity, spreadability, drug content, skin irritancy and cutaneous permeation.

Figure 6. Schematic presentation of emulgel penetration through skin. Reuse with permission from¹²². Licence number 5450130917355. Copyright 2013 Elsevier Ltd.

After 8h, 84% of bifonazole had been released from the microemulsion, proving a significant improvement in the penetration rate. The residence time of the drug with the skin was increased by the formulation. The study demonstrated that microemulsions-in-gel can modulate the drug release and sustain the kinetics.

4.2.2. Rationale design of emulsion in in gels. Optimization of the emulsion stability in presence of gels.

Gelling agents can be synthetic, semi-synthetic or natural. The latter has drawbacks such as sensitivity to microbial degradation phenomenon. Several synthetic or semi-synthetic agents are frequently used to prepare emulgels such as cellulose derivatives (for example, sodium carboxymethyl cellulose)¹²². Among the important parameters to obtain an efficient DDS using emulsions-in-gels, are the nature of the gels and its concentration. They can modify the release rate of the drug encapsulated in the emulsions. Thus, the amount of drug released is an inverse correlation with the gelling agent concentration. The gelling agent selection and concentration affect the rheological behaviour of the formulation and in particular its viscosity¹²⁹. The response of emulgels and specifically their stability upon phenomenon such as centrifugation, temperature cycles and one year of storage have been compared for emulgels made of different gelling agents (Carbopol, HPMC or Carbopol/HEC mix) to choose the best system to release clotrimazole an antimycotic drug, through the skin. It has been shown that the best formulations were with HPMC mixed with a low amount of Carbopol. This could be explained by a synergetic rheological response commonly encountered upon combination of these two gelling agents¹³⁰.

4.3. Lipid nanoparticles

4.3.1. Description of lipid nanoparticle-based systems.

Nanometric vehicles made from lipids are frequently used to deliver hydrophobic drugs into the skin or through it¹³¹. Among these nanoparticles (NPs), two categories are described, solid lipid nanoparticles (SLN) or nanostructured lipid carriers (NLC). Solid lipid nanoparticles are colloids from 50 to 1000 nm made of high fusion point lipids considered as a solid core at ambient temperature with a coating of surfactants¹³². Developed in the 90s, their small size and low polydispersity allow a good topical release⁷². Three types of structure can be obtained depending on the composition of the systems (lipids, active compounds, surfactants). The first structure described is a drug enriched core model, the second one is drug enriched shell model, and the last one is the homogeneous matrix model¹³³.

These vectors have different advantages. First, they can be used for both hydrophilic or hydrophobic drug release. For the hydrophilic compounds, however, low drug encapsulation is reported in the literature. Furthermore, encapsulating hydrophilic compounds requires using an organic solvent, which can limit the pharmaceutical applications^{134,135}. Thus, SLNs are mainly used to deliver hydrophobic compounds.

Second, SLNs have a good physical stability, low production cost and can be produced at the industrial scale using high-pressure homogenization¹³³. Third, the use of SLNs protects the drug from chemical degradation, especially against hydrolysis phenomena, as the drugs are less accessible in the SLNs¹³⁶. They also have an occlusive effect as they form films at the skin's surface that promote penetration of particles from 200 to 400 nm^{137,138,139}.

However, SLNs are difficult to disperse in an aqueous medium, and their solid matrix allows for time-extended release compared to classical nanoemulsions¹⁴⁰. SLNs are made from physiological lipids and do not require the use of organic solvent to be synthesized. This is an advantage in term of toxicity and biocompatibility compared to the use of polymeric nanoparticles¹⁴⁰.

The second category of lipid vectors used for the formulation of topical DDS is nanostructured lipid carriers (NLC). They are composed of a lipid fluid phase embedded in a solid lipid matrix or localized at the surface of solid platelets and the surfactant layer [32]. The spatial arrangement of lipids allows a better encapsulation efficiency in NLCs compared to SLNs as well as a better stability [39]. However, studies by Lippacher et al. showed that SLN dispersions have more elastic properties than NLCs with a similar amount of lipids¹⁴¹. SLNs and NLCs are good candidates for topical drug delivery applications for the same reasons: they have occlusive properties and their lipids can fuse with the SC. However, the liquid lipid phase of the NLCs can increase the amount of drug solubilized, and thus the payload of the system, inducing a higher quantity of drug release in the skin^{47,48}.

However, SLNs and NLCs have disadvantages to overcome: their low viscosity is not suitable with topical formulations and they need to be viscosified using hydrogels, for example. Indeed, several kind of hydrogels have been used in association with SLNs, among them Carbomer¹⁴², dextran¹⁴³ and xanthan⁷².

Capsaicinoid is a drug that limits chronic inflammatory disease but induces cutaneous irritation. To avoid this side effect, the active ingredient is encapsulated in nanocapsules dispersed in chitosan gels. In vivo skin irritation was performed by double-blind evaluation of skin erythema formation on 13 volunteers (males and females, aged 18 to 45 years). Capsaicinoid-loaded lipid nanocapsule gels did not cause erythema for up to 180 min after application to the skin, whereas the formulation without gel and/or nanocapsules did¹⁴⁴. SLN and NLC loaded with nitrendipine were also prepared in different gels (carbopol, xanthan, HPC or chitosan) in order to treat hypertension via transdermal administration¹⁴⁵. Excellent skin adhesion properties were observed with a better appearance and texture for Carbopol gels. Another example of use of SLNs in gel was published for the treatment of erectile dysfunction. Insoluble Avanafil was solubilised in SLNs dispersed in HPMC hydrogel¹⁴⁶. Ex-vivo permeation studies have validated the input in using these formulations for enhancing transdermal Avanafil delivery. SLNs formulated in HPMC hydrogels were also used to improve skin penetration of non-steroidal anti-inflammatory drugs and thus treat skin inflammation¹⁴⁷. The ex-vivo skin permeation studies showed that SLN-containing hydrogels increased drug permeation when comparing with commercial ibuprofen gels. Moreover, in vivo studies showed that hydrogels containing 16.6 times lower doses of ibuprofen formulated in SLNs had a similar anti-inflammatory activity to the commercial ibuprofen one.

Hydrogel Material	NPs Material	Drug loaded	Biomedical Application	Conclusions	Reference
Carbomer	SLN (Tristearin glyceride, soybean lecithin, and PEG400MS)	Triptolide	Anti-inflammatory	Increased transdermal absorption and enhanced anti-inflammatory activity	142
Dextran	SLN (Precirol, sodium cholate, poloxamer)	Ketoconazole	Antifungal	Easy spreadability, long shelf-life and reduce diffusion barrier of SC	143
Xanthan	SLN based on Compritol	Vitamin A	Wound healing	Prolonged delivery and enhanced delivery in deep layers	72
Carbopol, Xanthan, HPC, Chitosan	SLN (dynasan 114, DPPC, Tween 80)	Nitrendipine	Hypertension	Excellent adhering and constant release formulations	145
HPMC	SLN (Compritol, cholesterol, castor oil, Tween 80)	Avanafil	Erectil dysfunction	Enhanced transdermal delivery	146
HPMC	SLN (Compritol, Tween 80)	Etofenamate, Ibuprofen	Anti-inflammatory	Increased drug permeation and higher anti-inflammatory activity	147

Table 2: Summary of lipid nanoparticles-hydrogel systems used for dermal or transdermal biomedical applications

4.3.2. Rationale design of lipid vectors in gels systems. The compatibility of the ingredients, such as gelling agent and surfactants used, is paramount. It can affect the amount of drug encapsulated in the vehicles as well as the consistency and the stability of the formulation.

Drug solubility in the lipid nanoparticles

One parameter that has to be considered is the capacity of the drug to solubilize in the particles. Specifically, the active ingredient has to be soluble in the core. Thus, Patel et al. selected the solid lipids in their formulation depending on the aceclofenac solubility. They obtained a clear lipids solution, which melts under normal light when seen with naked eye¹⁴⁸. To viscosify the systems, the particles are dispersed in Carbopol 940P as it demonstrated good compatibility with NLCs and exhibited good spreading properties. Another study by Joshi used NLCs systems to encapsulate Valdecoxib, an anti-inflammatory drug, and tested different gelling agents such as Carbopol, Xanthan gum, and carrageenan. They selected the more appropriate gel depending on NLC dispersion, ease of preparation and appearance. They ultimately selected Carbopol as the more suitable pharmaceutical form due to its plastic rheological behavior¹⁴⁹.

Choice of the gelling agent

To rationalize the gelling agent choice for their systems, Müller et al. identified different parameters for investigation, including the charge of the particles. It is well established that nanoparticles undergo less aggregation when their zeta potential (ZP) is $> |30|$ mV¹⁵⁰. NP-based lipids are generally negatively charged¹⁵¹, and the dispersion ZP can be measured with or without the gels to predict the formulation stability. The incorporation of negatively charged NPs loaded in chitosan gels led to the neutralization of the surface charge of the NPs, making the formulations unstable due to the aggregation

phenomenon. These stability issues have been observed in Carbopol formulations because of their carboxylic moieties, which have to be neutralized with NaOH to trigger gel formation. The ZP of nanoparticles is reduced by the Na⁺ ions present as electrolytes in the medium-inducing aggregation

¹⁵². Aggregation issues are often reported when NLC or SLN systems are used¹⁵³. These two types of dispersions present few physical and chemical modifications when they are dispersed in hydrogels with little to no charge.

Rheological behavior

Another important design feature is to globally study the rheological properties of a system, which means studying rheology with the drug, the lipid nanoparticles and the gels all together. The interactions between the components of the formulation can lead to consistency modification and changes in the rheological behavior, which are important parameters for potential topical applications. A complete study made by Souto et al. showed that by increasing the lipid quantity in the hydrogel formulations, the flow characteristics changed. The flow curves of pure hydrogels investigated showed a weaker structure than hydrogels containing SLNs or NLCs. These systems with high lipid content are thixotropic. Hydrogels prepared from HEC and Chitosan are more liquid and thus might not have a good consistency for topical administrations. Lipid nanoparticles interact with Xanthan gum and Carbopol 934, which modifies the hydrogel's rheological properties. In the appropriate ratio, formulations are compatible with the preparation of semi-solid, topical drug delivery systems. The rheological behavior of xanthan gels containing lipids is affected by applied shear stress compared with Carbopol hydrogels containing the same lipids¹⁵⁴.

4.4. Liposomes and flexible vesicles

4.4.1. Description of vesicular delivery systems. The vehicles described in this section are vesicular systems. Vesicles are colloidal structures made of a hydrophilic cavity delimited by a membrane made of a concentric bilayer. This membrane can be made of amphiphilic molecules such as polymers, lipids or surfactants. Depending on the specificity of the vesicles, such as the membrane composition and solvent, the vesicles can be classified as liposomes, ethosomes, niosomes or transfersomes.

Liposomes are among the most studied systems for topical delivery purposes. They are lipidic vesicular systems made of one or more bilayers of phospholipids which enclose a liquid core. These objects self-assemble in water under mild conditions. Lipids can adhere to the SC or dissolve into its lipidic structure to promote drug permeation in the dermis (Figure 7-A, Figure 7-C). However, it has been shown that liposomes do not penetrate in the deeper layers of the skin and remain in the SC due to a lack of deformability^{155,156,157}. Furthermore, the preparation of liposomes implies the use of organic solvent that could induce toxicity issues and submit the drugs to energetical processes that cause stability issues. Due to these limitations, other vesicular systems have been developed as drug delivery systems to target the dermis¹⁷.

When ethanol is present in the water phase, the resulting structures are named ethosomes. They are smaller than liposomes and exhibit higher encapsulation capacities for both hydrophilic and hydrophobic species¹⁵⁸. The efficiency of ethosomes as dermal delivery systems is due to the permeation-enhancing effect of ethanol, and the improved fluidity of the lipids present in both the SC and the membrane of the ethosomes. These effects promote the diffusion of ethosomes between the cells of the SC towards the deep layers of the skin (Figure 7-B or 7-C)^{159,160}. However, ethanol can induce irritation and toxicity limitations.

Niosomes are vectors similar to liposomes, but with a membrane made of non-ionic surfactants and cholesterol, which create uni- or multi-lamellar bilayers. Niosomes are more stable and cheaper than liposomes and easier to prepare¹⁶¹. Furthermore, the surfactants used for the membrane increase the fluidity of the lipids of the SC, as they can partly fuse with it and some surfactants can act as permeation enhancers (Figure 7-C)^{159,160,162}. In addition, they can prolong circulation of drugs in plasma, and can modify drug stability and distribution¹⁶³. However, the mechanism of niosomes penetration is comparable to liposomes penetration, in that they enter mainly the SC and their penetration to the viable epidermis and the dermis is limited. The cholesterol induces an increase in the membrane rigidity that limits the penetration of niosomes in the deepest layer of the skin (Figure 7-A). Another limitation to the use of niosomes is the presence of surfactants, which is a controversial concern as they can induce irritation issues¹⁶⁴.

Finally, transfersome lipid vesicular systems are designed to reach the deepest layer of the skin (Figure 7-D). Thus, they have the capability to be ultra-deformable and reformable, allowing them to pass through biological membranes such as SC¹⁶⁵. They can also reach the systemic circulation without alteration of their structure and can enter tight pores with specific mechanisms (Figure 7-E).

To achieve the bilayer membrane elasticity, an edge activator specie is inserted between the phospholipids. This edge activator is often made of a single-stranded surfactant¹⁶⁶.

However, the transfersomes have the same limitations as liposomes due to preparation techniques involving organic solvent.

Figure 7. Possible mechanisms of action of vesicular systems as skin drug delivery systems. (A) The free drug mechanism, (B) Vesicle adsorption to and/or fusion with the stratum corneum (SC), (C) The penetration enhancing process of vesicular components, (D) Intact vesicle penetration into or into and through the intact skin, and (E) The penetration of the vesicles through a hair follicle. Adapted from¹⁶⁷ (Future Journal of Pharmaceutical Sciences)

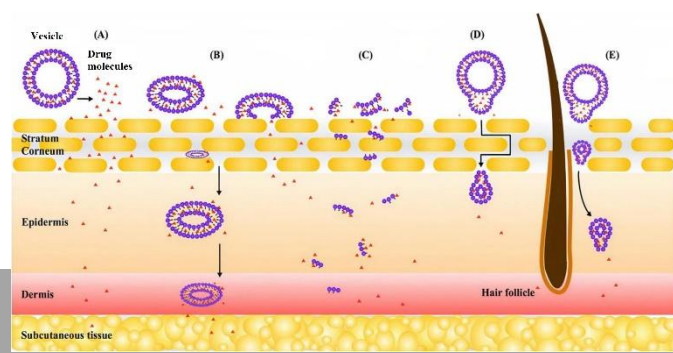
To summarize, vesicular systems have several advantages¹⁷. The vectors can cross the skin or act as reservoirs or local depots for sustained release purposes¹⁶⁸. The objective of using them in formulations can be to administer a drug locally or to target the systemic circulation¹⁶⁹. These vehicles can allow the encapsulation of hydrophobic drugs (in their membranes) or hydrophilic ones (in their core)¹⁷⁰. Their components have to be chosen according to the application targeted: for example, to be biocompatible.

Furthermore, vesicular systems can be designed to perform controlled-release, and can promote transdermal absorption and bioavailability of the drugs^{171,172}. Depending on the vesicle properties and design, several mechanisms of drug release can be achieved, and specific layers of the skin can be targeted (Figure 7)¹⁷³. In addition, vesicular systems are sensitive to the hydration gradient through the skin, which propels it through transcutaneous channels¹¹. However, vesicles solutions have a low viscosity and have to be formulated into a suitable pharmaceutical form for topical applications.

To overcome this issue, vesicular solutions are often dispersed in hydrogels. The extension of the contact time between the vehicles and the skin induced by the gels improves the permeation of the drugs into the skin, and thus their bioavailability^{171,172}. The applications targeted with these systems are used to treat skin diseases impacting the immune system, allergic diseases, auto-immune diseases or diseases reacting to inflammatory mechanisms. They are also investigated to treat chronic allergic dermatitis.

Many examples of liposomes-in-gels systems are described. For example, liposomes made of different compositions (tocopherol acetate, cholesterol, phospholipon, Phosphatidylcholine, etc.) and loaded with different drugs (18 β -glycyrrhetic acid, betamethasone valerate or diflucortolone valerate, C-Phycocyanin, indomethacin) are described, and are dispersed in hydrogels of various structures such as Carbomer 971, Carbopol 940, glycerin, Xanthan^{174,175,176,137}. These systems show promise as they have simultaneously demonstrated an appropriate pharmaceutical form and good anti-inflammatory activities, have reduced clinical scores by reducing edema and erythema, or improved drug transport through the skin.

Most of the time, the various drugs-in-liposome-in-gels formulations are evaluated compared to drug-in-gels or compared to already available commercial products. They are also tested in different models such as dermatitis model on the ear^{174,175}, rat model¹⁷⁶ or human trials¹³⁷. Finally, extended retention times and higher accumulation of drug are reported



for liposome-in-gel formulations compared to vehicles alone¹⁷⁵.

Other vesicle-in-gel systems have been investigated. For example, systems made of niosomes-in-hydrogels are described. Kaur et al. proved a 6.5-fold higher deposit of methotrexate (an antipsoriatic drug) in the deep layers of the skin and in muscles when the drug was encapsulated in niosomal chitosan hydrogels compared to the commercial formulation of the drug in carbopol¹⁷⁷. The reduction in psoriasis severity after 12 weeks of niosomal methotrexate gel topical application was threefold higher and with better clinical efficacy, tolerability and patient compliance¹⁷⁷.

Furthermore, many topical drug delivery systems imply transfersomes-in-gels to target the deeper layers of the skin. For instance, non-occlusive and non-invasive transdermal administration of therapeutic proteins using transfersomes is described. Thus, the incorporation of insulin molecules into transfersomes (transfersulin) made of an ethanolic SPC solution, with the appropriate amount of sodium collate as edge-active molecule, leads to a considerable insulin transport through the skin and into the blood stream in mice and to a lesser extent in humans¹⁷⁸. The driving force for insulin transport is the local water loss gradient across the skin barrier.

Transfersomes could also be designed to achieve a localized and high drug concentration at the application site and deep into the dermis. For example, transfersomes of span 80 and soya lecithin are easily dispersed in carbopol gels; these systems have proved an enhanced skin delivery of sertraline, an antidepressant drug¹⁷⁹. No skin irritation was found after transdermal application of these gel formulations.

4.4.2. Rationale design of vesicle-in-gel systems. To design suitable drug delivery systems using vesicles-in-gel, different parameters have a preponderant effect on the system performance. These parameters are discussed in the following section. To master the formulations and optimize their design, all these parameters have to be investigated.

Effect of the vesicles-gels interaction

Many times, the effects of the addition of vector-in-gel structures is not described in the studies. However, introduction of vehicles has an effect on the rheological behavior of the gels, thus influencing the diffusion of the vesicles. For example, the introduction of positively charged liposomes in Natrosol (HEC) gels induces a thickening effect¹⁸⁰. Furthermore, it has been proven that liposomes can decrease gelation time of gels when the gelification is done in situ, which means in presence of the vectors. For example, negatively charged liposomes can decrease gelation capacity of chitosan due to electrostatic interactions with ammonium ions of the chitosan¹⁸¹.

Effect of vesicles properties

First, depending on the type of lipids used in the liposome's composition, the kinetics of release can be tuned. Indeed, these changes impact the amount of drug loaded and the rigidity of the membrane. For example, Antimisariis's team prepared liposomes composed of phosphatidylcholine (PC) or

distearoyl-glycerol-PC and cholesterol (DSPC/Chol) in different proportions. By changing the liposome composition, it can be concluded that the vesicles with fluid-flexible membranes exhibit faster hydrophilic drug release, but the payloads of the systems are different. Thus, at similar payload, no difference is observed in the kinetics of release. The dominant factor to control the release rate is the encapsulated amount and not the rigidity of the membrane¹⁸². However, the rigidity of the membranes of the vesicles has an impact on the gel's properties. The Antimisariis team has proven that at high liposome loading in the gel, if the membrane is fluid (flexible), the gel's rheological properties will not be changed. Conversely, with rigid membranes the systems will be frozen and the viscosity increases at low shear rate. At high shear rates, gels loaded with rigid liposomes have better flow properties. In this study, the membrane composition and the amount of vesicles encapsulated in the gels are determining factors affecting the rheological properties of gels, whereas the size of the liposomes is not paramount¹⁸³. Chemical permeation enhancers such as glycerol and ethanol can be introduced in the formulation of vesicles, such as sugar-derived vesicles to modify their membrane rigidity in order to promote SC penetration. These nanocarriers introduced in HEC gels reach the optimal texture for topical applications¹⁸⁴.

Effect of the drug encapsulated on its encapsulation and release

The payload is correlated to the physical and chemical properties of the drug molecules, especially their Log P and thus their solubility. Depending on the drug hydrophobia and on the preparation method, the amount of encapsulated drug in the vesicles changes^{52,185}. For example, Marianecchi et al. studied niosomes (Tween 20/cholesterol 1:1) loaded with different molecules and dispersed in Xanthan/Locust bean gels¹⁸². The presence of niosomes has a major effect on improving the encapsulation of insoluble drugs.

Furthermore, release of the different molecules from formulations such as niosomes-in-gels or liposomes-in-gels has been compared in several studies depending on drug hydrophilic balance^{52,182}. Mourtas et al. have shown that the lack of solubility can limit the release of the hydrophobic compound (griseofulvin) from the liposome-in-gels system compared to the release of soluble hydrophilic species such as calcein. However, the amount of non-soluble drug released from niosomes is improved compared to free drug-in-gels, which is limited by solubility issues. In the case of the hydrophilic species, the fitted release kinetic curves highlight a mechanism of diffusion. Thus, the presence of liposomes decreases the release kinetics as the step of diffusion out of the vectors is added in the release process: liposomal entrapment of drugs sustains their release. These results have been proved in different studies^{112,186,187}.

To release a hydrophobic drug, the rate-determining step is the diffusion of the molecule out of the vesicle, but the exact mechanisms are unknown. Once out of the vesicles, the free drug diffuses rapidly out of the gels. The fitted release curves confirm a more complex mechanism than simple diffusion explained by solubility effects and the hydrophobic properties

Hydrogel Material	NPs Material	Drug loaded	Biomedical Application	Conclusions	Reference
Carbomer 971P	Liposomes (Phospholipon 90H, tocopherol acetate, Tween 80)	Glycyrrhetic acid	Anti-inflammatory on allergic contact dermatitis	Increased anti-inflammatory activity	174
Chitosan	Liposomes (Lipoid S100, Phospholipon 90G, cholesterol, Tween 80)	Betamethasone 17-valerate, Diflucortolone valerate	Anti-inflammatory on atopic dermatitis	Increased anti-inflammatory activity	175
Carbopol 940 in glycerine	Liposomes (Phosphatidylcholine, cholesterol)	C-phycocyanin	Anti-inflammatory	Increased anti-inflammatory activity	176
Chitosan	Niosomes	Methotrexate	Psoriasis	Better absorption and penetration through skin. Improved clinical efficacy and tolerability	177
Carbopol 940	Transfersomes (soya lecithin, Span80)	Sertraline	Depression	Enhanced skin delivery. Increased antidepressant activity	179

Table 3: Summary of vesicles-hydrogel systems used for dermal or transdermal biomedical applications

of the drug. Furthermore, the addition of drug-in-vesicles-in-gels can modify the rheological properties of the gels and influence the diffusion of the vehicles in their matrix. In addition, by decreasing the size of a drug, using griseofulvin instead of calcein, the release rate is increased as the drug diffuses rapidly out of the gel due to its smaller size¹⁸².

To conclude, the formulation of vesicle-in gel systems is promising for dermal or transdermal drug delivery. However, it is important to design the system in its totality: in addition to the nature of the lipids, the properties of the couple lipid/drug have to be controlled. The drug loaded can modify the vesicle properties (membrane rigidity, zeta potential, amount of drug loaded, kinetics of release), which can subsequently modify the gel behavior. The appropriate design of these systems can lead to a good control of the kinetics of release and of the layer of the skin targeted.

Two determinant steps have been identified in the release mechanism—release of drugs from the vehicles and diffusion in the gel—and their relative importance is modulated by the system parameters. Nevertheless, it has been previously demonstrated that maximum loading amounts of amphiphilic or lipophilic drugs-in-liposomes are linearly correlated with their log P values (lipid/aqueous partition coefficient).

Therefore, the log P value of each candidate drug is the first characteristic that should be taken into account when designing liposomal gels¹⁸².

4.5. Other drug delivery systems in gels

Nanocapsules are vesicular systems made of a liquid core (most of the time an oil) surrounded by a thin polymer layer¹⁸⁸. In aqueous formulations, the polymers used are homopolymers or copolymers where the hydrophilic moieties are facing outward¹⁸⁸. These systems are mainly used to encapsulate hydrophobic drugs and to target the upper layer of the skin, as the penetration of the capsules deeper than the SC is limited^{189,190}. Indeed, the capsules form a thin film on top of the skin that allows sustained release of drugs. For example, their efficiency to improve the retention of dioctylmethoxycinnamate, a sunscreen lipophilic molecule, in the SC have been proven¹⁹¹. However, their utilisation as DDS is limited due to their method of preparation. It can be difficult to produce them at the industrial scale, and purification issues induce the presence of residues which can be toxic¹⁹².

A few examples of capsules associated with gels are described

Hydrogel Material	NPs Material	Drug loaded	Biomedical Application	Conclusions	Reference
PEG-NH ₂ and PEG-NHS	Polymeric microcapsules (PEG-PLGA)	Diclofenac sodium	Anti-inflammatory	Good biocompatibility, remarkable skin-adhesion and ultrasound controlled delivery	193
Xanthan, konjac glucomannan	Polymeric NPs (polydopamine)	Dopamine	Wound healing	Increased rate of wound closure. Reduced inflammation and improved epidermal regeneration	194
Pluronic F-127	Polymeric NPs (PLGA)	Platelet lysate	Wound healing	Prolonged release. Increased tissue regeneration	195
Polyacrylamine	Dendrimer NPs (PAMAM G4)	Platensimycin	Antibacterial	Increased antibacterial activity	196
Polyacrylamine	Inorganic NPs (mesoporous silica NPs)	Rhodamine 6G	Adhesive patch	Enhanced adhesiveness to skin	197

Table 4: Summary of other drug delivery systems-hydrogel systems used for dermal or transdermal biomedical applications

in the literature. Capsules can also be associated with physical permeation enhancers. Thus, transdermal administration of diclofenac sodium (DS) can be performed with a responsive delivery system associated with LFU. Accomplishing this requires embedding DS-loaded polyester microcapsules in PEG hydrogels patches. The rational design of the system gives the hydrogel patches good biocompatibility, cutaneous adhesiveness and a well-controlled responsive system to deliver DS upon LFU exposure. The use of LFU to trigger the release allows for the simultaneous delivery of the active ingredient and chemical permeation enhancers, which helps the drug to penetrate the SC faster. Ex vivo and in vivo studies prove the subcutaneous penetration of DS, which is triggered by LFU exposure from a transdermal drug delivery system made of a hydrogel matrix¹⁹³.

Nanospheres or polymeric nanoparticles (NPs) are solid colloidal particles composed of polymers with a diameter of about 100 to 200 nm. The drug is entrapped in the polymeric matrix or adsorbed on the surface of the nanoparticle. The polymers used for the formation of the nanoparticles are often biocompatible, and can be natural biopolymers (e.g. chitosan or xanthan), or synthetic polymers (e.g. polyacrylates or poly(lactic-co-glycolic acid)) PLGA¹⁹⁵. As other drug delivery systems, nanospheres may be used as reservoirs to control drug release in the deeper layers of the skin. Some examples of polymeric nanoparticles incorporated in hydrogels are described in the literature for biological applications using different routes of administration, and in particular cutaneous delivery¹⁹⁸. Polydopamine nanoparticles loaded in xanthan and konjac glucomannan gums have been used for skin tissue repairing on rats' bacteria-infected wounds¹⁹⁴. The results demonstrate that the NPs loaded in the hydrogel can promote the closure of infected wounds by reducing inflammation and increasing tissue regeneration. Another smart system was developed for wound healing, using a thermo-reversible hydrogel made of Pluronic F-127¹⁹⁵. The inclusion of PLGA nanoparticles in this stimuli-responsive gel offers a prolonged and controlled release of the platelet lysate encapsulated drug. It also provides in vivo in mice a faster wound healing and epidermal regeneration. An excellent antibacterial activity has also been obtained using platensimycin-loaded PAMAM dendrimers incorporated in a polyacrylamide gel¹⁹⁶.

Inorganic nanoparticles can also be charged with drugs, covalently attached on the surface of the particle or incorporated in pores inside the structure of the nanoparticle. Several systems made of inorganic nanoparticles have been developed for dermal or transdermal drug delivery, as metallic gold NPs, titanium dioxide, calcium phosphate or silica nanoparticles¹⁹⁹. However, few examples of inorganic nanoparticles incorporated in hydrogels have been published for transdermal drug delivery. Kim et al. have developed biocompatible patches based on extra-large pore mesoporous silica NPs included in a polyacrylamide/polydopamine hydrogel with an enhanced adhesiveness¹⁹⁷.

5. Conclusion

Among the various pharmaceutical formulations used for dermal and transdermal administration of drugs, hydrogels are one of the most acceptable systems in terms of physical properties and patient acceptability. Through this review, we have discussed the recent developments in hydrogel formulations and their major advantages and drawbacks as drug delivery systems for dermal and transdermal administration. All the important parameters to reach a suitable topical form, including spreadability, rheology, nature of the polymer chains, occlusivity and release mechanisms of the active ingredient are discussed. They can have a major effect on the acceptability of the formulation by the patient (spreadability, rheology), but also in its effectiveness. Indeed, the occlusive effect can improve the quantity of drug delivered to the skin, the nature of polymer chains can impact the costs and the interaction of the drug with both the hydrogel and the skin. In addition, the release mechanisms can impact the quantity of drug released but also its kinetics. The effect of drug concentration and physical and chemical parameters of the drugs on its release are described, as they can be tuned to improve the drug permeation into the skin. Indeed, the interaction of the drug with the hydrogels, as well as the affinity of both the active ingredient and the gel for the skin, influence the capacity of the drug to penetrate different skin layers.

In order to further increase skin penetration of the drugs and maximize drug delivery, chemical and physical permeation enhancers can be used in combination with hydrogels. Softener alternatives using nanovectors in association with hydrogels are also discussed. The advantages and drawbacks of the different nanosystems (emulsions, lipid nanoparticles, liposomes, vesicles, capsules, polymeric and inorganic nanoparticles) are presented. These systems allow the synergetic effect of both the hydrogel and the vector to create an optimized dermal or transdermal drug delivery system. Several innovative studies investigating vector-in-gel systems are described.

For drug formulation, this study is an overview of the technological solutions using hydrogels, which can be investigated to design the best formulation system for a specific active ingredient. It emphasizes the important parameters that have to be studied to master and control the formulations.

Author Contributions

Writing—original draft preparation, H.L.; Writing—review and editing, M.B.; Supervision, M.B.; Project administration, M.B.; Funding acquisition, M.B. All authors have read and agreed to the published version of the manuscript.

Acknowledgements

HL was funded with a two-year postdoctoral fellowship from by the “Agence Nationale de la Recherche” (program ANR-18-CE18-0011). The APC was funded by institutions (CNRS and the University of Toulouse).

Notes and references

- S. K. Sah, A. Badola and B. K. Nayak, *Indian Journal of Pharmaceutical and Biological Research*, 2018, **5**, 25–33.
- K. Kathe and H. Kathpalia, *Asian Journal of Pharmaceutical Sciences*, 2017, **12**, 487–497.
- G. W. Ashley, J. Henise, R. Reid and D. V. Santi, *Proceedings of the National Academy of Sciences*, 2013, **110**, 2318 LP – 2323.
- R. K. Chang, A. Raw, R. Lionberger and L. Yu, *AAPS Journal*, 2013, **15**, 41–52.
- I. P. Harrison and F. Spada, *Pharmaceutics*, 2018, **10**, 71–84.
- B. W. Barry, in *Marcel Dekker, New York/Basel.*, John Wiley & Sons, Ltd, 1983.
- T. W. Prow, J. E. Grice, L. L. Lin, R. Faye, M. Butler, W. Becker, E. M. T. Wurm, C. Yoong, T. A. Robertson, H. P. Soyer and M. S. Roberts, *Advanced Drug Delivery Reviews*, 2011, **63**, 470–491.
- E. Christophers and A. M. Kligman, *The Journal of investigative dermatology*, 1964, **42**, 407–409.
- E. Christophers, *The Journal of investigative dermatology*, 1971, **56**, 165–169.
- A. S. Michaels, S. K. Chandrasekaran and J. E. Shaw, *AIChE Journal*, 1975, **21**, 985–996.
- G. Cevc and G. Blume, *BBA - Biomembranes*, 1992, **1104**, 226–232.
- M. A. Lampe, M. L. Williams and P. M. Elias, *Journal of Lipid Research*, 1983, **24**, 131–140.
- B. W. Barry, *Journal of Controlled Release*, 1987, **6**, 85–97.
- R. J. Scheuplein, *The Journal of investigative dermatology*, 1965, **45**, 334–346.
- W. J. ALBERY and J. HADGRAFT, *Journal of Pharmacy and Pharmacology*, 1979, **31**, 140–147.
- A. C. Willia and B. W. Barry, *Pharmaceutical Research: An Official Journal of the American Association of Pharmaceutical Scientists*, 1991, **8**, 17–24.
- C. Richard, S. Cassel and M. Blanzat, *RSC ADVANCES*, 2021, **11**, 442–451.
- N. Otberg, H. Richter, H. Schaefer, U. Blume-Peytavi, W. Sterry and J. Lademann, *Journal of Investigative Dermatology*, 2004, **122**, 14–19.
- R. H. Guy and J. Hadgraft, *Mathematical models of percutaneous absorption.*, Marcel Dekker Inc., New York, Percutaneo., 1989.
- M. A. Bolzinger, S. Briançon, J. Pelletier and Y. Chevalier, *Current Opinion in Colloid and Interface Science*, 2012, **17**, 156–165.
- H. Benson, *Current Drug Delivery*, 2005, **2**, 23–33.
- J. D. Bos and M. M. H. M. Meinardi, *Experimental Dermatology*, 2000, **9**, 165–169.
- B. W. Barry and A. J. Grace, *Journal of Pharmaceutical Sciences*, 1972, **61**, 335–341.
- S. Devaux, A. Castela, E. Archier, A. Gallini, P. Joly, L. Misery, S. Aractingi, F. Aubin, H. Bachelez, B. Cribier, D. Jullien, M. Le Maître, M. A. Richard, J. P. Ortonne and C. Paul, *Journal of the European Academy of Dermatology and Venereology*, 2012, **26**, 61–67.
- K. C. Ashara, J. S. Paun, M. M. Soniwala, J. R. Chavada and N. M. Mori, *Asian Pacific Journal of Tropical Disease*, 2014, **4**, S27–S32.
- A. Gupta, A. Mishra, A. Singh, V. Gupta and P. Bansal, *Drug Invention Today*, 2010, **2**, 250–253.
- L. Lacalendola Tundisi, F. Croisfelt, P. Mazzola, J. Artem Ataide, E. Silveira, A. Jozala, E. Tambourgi and E. B. Souto, *Journal of Materials Science*, 2019, **54**, 10963–10983.
- V. Nouri, M. Pontes De Siqueira Moura, B. Payre, O. De Almeida, C. Déjugnat, S. Franceschi and E. Perez, *Soft Matter*, 2020, **16**, 2371–2378.
- A. Vintiloiu and J. C. Leroux, *Journal of Controlled Release*, 2008, **125**, 179–192.
- N. A. Peppas, P. Bures, W. Leobandung and H. Ichikawa, *European Journal of Pharmaceutics and Biopharmaceutics*, 2000, **50**, 27–46.
- K. Rehman and M. H. Zulfakar, *Drug Development and Industrial Pharmacy*, 2014, **40**, 433–440.
- M. Suzuki, C. Setoguchi, H. Shirai and K. Hanabusa, *Chemistry – A European Journal*, 2007, **13**, 8193–8200.
- R. Oda, I. Huc and S. J. Candau, *Angewandte Chemie International Edition*, 1998, **37**, 2689–2691.
- S. Malik, S. K. Maji, A. Banerjee and A. K. Nandi, *J. Chem. Soc. Perkin Trans. 2*, 2002, 1177–1186.
- J. F. Toro-Vazquez, J. A. Morales-Rueda, E. Dibildox-Alvarado, M. Charó-Alonso, M. Alonzo-Macias and M. M. González-Chávez, *Journal of the American Oil Chemists’ Society*, 2007, **84**, 989–1000.
- C. M. Garner, P. Terech, J.-J. Allegraud, B. Mistrot, P. Nguyen, A. de Geyer and D. Rivera, *J. Chem. Soc. Faraday Trans.*, 1998, **94**, 2173–2179.
- J.-M. Guenet, *Organogels: Thermodynamics, Structure, Solvent Role, and Properties*, 2016.
- Y. E. Shapiro, *Progress in Polymer Science (Oxford)*, 2011, **36**, 1184–1253.
- A. S. Panwar, N. Upadhyay, M. Bairagi, S. Gujar, G. Darwhekar and D. Jain, *Asian Journal of Pharmacy and Life Science*, 2011, **1**, 333–343.
- C. Sarisozen, I. Vural, T. Levchenko, A. A. Hincal and V. P. Torchilin, *Drug Delivery*, 2012, **19**, 169–176.
- J. F. G. M. HURKMANS, H. E. BODDÉ, L. M. J. VAN DRIEL, H. VAN DOORNE and H. E. JUNGINGER, *British Journal of Dermatology*, 1985, **112**, 461–467.
- N. Trookman, R. Rizer, R. Ford and V. Gotz, *Journal of the American Academy of Dermatology*, 2008, **58**, AB52.
- M. A. Ruiz Martinez, J. López-Viota Gallardo, M. M. de Benavides, J. de Dios García López-Duran and V. Gallardo Lara, *International Journal of Pharmaceutics*, 2007, **333**, 17–23.
- A. Martínez-Ruvalcaba, E. Chornet and D. Rodrigue, *Carbohydrate Polymers*, 2007, **67**, 586–595.
- N. A. Peppas and A. Singh, *Advanced Materials*, 2014, **26**, 6530–6541.
- M. Caldorera-Moore and N. A. Peppas, *Advance*, 2009, **61**, 1391–1401.
- D. A. Gyles, L. D. Castro, J. O. C. Silva and R. M. Ribeiro-Costa, *European Polymer Journal*, 2017, **88**, 373–392.
- W. Tanan, J. Panichpakdee and S. Saengsuwan, *European Polymer Journal*, 2019, **112**, 678–687.
- M. J. Jamadar and R. H. Shaikh, *Journal of pharmaceutical research and education*, 2017, **1**, 201–224.
- X. Xu, B. Bai, C. Ding, H. Wang and Y. Suo, *Industrial and Engineering Chemistry Research*, 2015, **54**, 3268–3278.
- E. M. Ahmed, *Journal of Advanced Research*, 2015, **6**, 105–121.
- C. Marianecchi, M. Carafa, L. Di Marzio, F. Rinaldi, C. Di Meo, F. Alhaique, P. Matricardi and T. Coviello, *J Pharm Pharmaceut Sci*, 2011, **14**, 336–346.
- H. Labie, A. Perro, V. Lapeyre, B. Goudeau, B. Catargi, R. Auzély and V. Ravaine, *Journal of Colloid and Interface Science*, 2019, **535**, 16–27.

- 54 K. Rehman, M. C. I. M. Amin and M. H. Zulfakar, *Journal of Oleo Science*, 2014, **63**, 961–970.
- 55 A. S. Hoffman, *Advanced Drug Delivery Reviews*, 2012, **64**, 18–23.
- 56 E. Pérez, A. Fernández, R. Olmo, J. M. Teijón and M. D. Blanco, *Colloids and Surfaces B: Biointerfaces*, 2014, **116**, 247–256.
- 57 Z. Zhang, Z. He, R. Liang, Y. Ma, W. Huang, R. Jiang, S. Shi, H. Chen and X. Li, *Biomacromolecules*, 2016, **17**, 798–807.
- 58 A. Garg, D. Aggarwal, S. Garg and A. K. Singla, *Pharmaceutical Technology North America*, 2002, **26**, 84–105.
- 59 B. Vennat, D. Gross and A. Pourrat, *Drug Development and Industrial Pharmacy*, 1992, **18**, 1535–1548.
- 60 M. T. Islam, N. Rodríguez-Hornedo, S. Ciotti and C. Ackermann, *Pharmaceutical Research*, 2004, **21**, 1192–1199.
- 61 T. Cerchiara, B. Luppi, F. Bigucci, I. Orienti and V. Zecchi, *Journal of Pharmacy and Pharmacology*, 2002, **54**, 1453–1459.
- 62 S. Mourtas, S. Duraj, S. Fotopoulou and S. G. Antimisiaris, *Colloids and Surfaces B: Biointerfaces*, 2008, **61**, 270–276.
- 63 M. Bousmina, *Rheologica Acta*, 1999, **38**, 73–83.
- 64 L. Noble, A. I. Gray, L. Sadiq and I. F. Uchegbu, *International Journal of Pharmaceutics*, 1999, **192**, 173–182.
- 65 L. Kircik, *Journal of drugs in dermatology: JDD*, 2012, **11**, 180–184.
- 66 K. A. Greive and T. M. Barnes, *Australasian Journal of Dermatology*, 2016, **57**, e39–e45.
- 67 B. Yentzer, F. Camacho, T. Young, J. Fountain, A. Clark and S. Feldman, *Journal of Drugs in Dermatology*, 2010, **9**, 324–329.
- 68 L. Kircik and J. Rosso, *Journal of drugs in dermatology: JDD*, 2007, **6**, 718–722.
- 69 D. Kerney, R. Ford and V. Gotz, *Cutis; cutaneous medicine for the practitioner*, 2011, **88**, 18–24.
- 70 K. S. Paudel, M. Milewski, C. L. Swadley, N. K. Brogden, P. Ghosh and A. L. Stinchcomb, *Therapeutic Delivery*, 2010, **1**, 109–131.
- 71 A. Nangia, S. Patil, B. Berner, A. Boman and H. Maibach, *International Journal of Pharmaceutics*, 1998, **170**, 33–40.
- 72 V. Jennings, A. Gysler, M. Schäfer-Korting and S. H. Gohla, *European Journal of Pharmaceutics and Biopharmaceutics*, 2000, **49**, 211–218.
- 73 N. Bhattarai, J. Gunn and M. Zhang, *Advanced Drug Delivery Reviews*, 2010, **62**, 83–99.
- 74 G. M. Cruise, D. S. Scharp and J. A. Hubbell, *Biomaterials*, 1998, **19**, 1287–1294.
- 75 M. C. I. Mohd Amin, N. Ahmad, N. Halib and I. Ahmad, *Carbohydrate Polymers*, 2012, **88**, 465–473.
- 76 S. M. Ali and G. Yosipovitch, *Acta Dermato-Venereologica*, 2013, **93**, 261–267.
- 77 C. A. Carmona-Moran, O. Zavgorodnya, A. D. Penman, E. Kharlampieva, S. L. Bridges, R. W. Hergenrother, J. A. Singh and T. M. Wick, *International Journal of Pharmaceutics*, 2016, **509**, 465–476.
- 78 C. C. Lin and A. T. Metters, *Advanced Drug Delivery Reviews*, 2006, **58**, 1379–1408.
- 79 J. Yu, J. Wang, Y. Zhang, G. Chen, W. Mao, A. R. Kahkoska, J. B. Buse, R. Langer and Z. Gu, *Nat Biomed Eng*, 2020, **4**, 499–506.
- 80 D. S. Jones, A. D. Woolfson and A. F. Brown, *International Journal of Pharmaceutics*, 1997, **151**, 223–233.
- 81 A. Concheiro and C. Alvarez-Lorenzo, *Advanced Drug Delivery Reviews*, 2013, **65**, 1188–1203.
- 82 V. K. Singh, D. Qureshi, S. K. Nayak and K. Pal, in *Woodhead Publishing Series in Biomaterials*, eds. K. Pal and I. B. T.-P. G. Banerjee, Woodhead Publishing, 2018, pp. 265–282.
- 83 H. B. Eral, V. López-Mejías, M. O'Mahony, B. L. Trout, A. S. Myerson and P. S. Doyle, *Crystal Growth and Design*, 2014, **14**, 2073–2082.
- 84 A. V. Kabanov and S. V. Vinogradov, *Angew Chem Int Ed Engl.*, 2010, **48**, 5418–5429.
- 85 Y. Sun, L. Du, Y. Liu, X. Li, M. Li, Y. Jin and X. Qian, *International Journal of Pharmaceutics*, 2014, **469**, 31–39.
- 86 J. F. Rosa dos Santos, C. Alvarez-Lorenzo, M. Silva, L. Balsa, J. Couceiro, J. J. Torres-Labandeira and A. Concheiro, *Biomaterials*, 2009, **30**, 1348–1355.
- 87 I. F. Almeida, A. R. Fernandes, L. Fernandes, M. R. Pena Ferreira, P. C. Costa and M. F. Bahia, *Pharmaceutical Development and Technology*, 2008, **13**, 487–494.
- 88 G. J. Rhee, J. S. Woo, S. J. Hwang, Y. W. Lee and C. H. Lee, *Drug Development and Industrial Pharmacy*, 1999, **25**, 717–726.
- 89 V. K. Singh, D. Qureshi, S. K. Nayak and K. Pal, in *Woodhead Publishing Series in Biomaterials*, eds. K. Pal and I. B. T.-P. G. Banerjee, Woodhead Publishing, 2018, pp. 265–282.
- 90 A. Almomen, S. Cho, C. H. Yang, Z. Li, E. A. Jarboe, C. M. Peterson, K. M. Huh and M. M. Janát-Amsbury, *Pharmaceutical Research*, 2015, **32**, 2266–2279.
- 91 N. Jibry, R. K. Heenan and S. Murdan, *Pharmaceutical Research*, 2004, **21**, 1852–1861.
- 92 E. Larrañeta, S. Stewart, M. Ervine, R. Al-Kasasbeh and R. F. Donnelly, *Journal of Functional Biomaterials*, 2018, **9**, 1.
- 93 H.-Y. Thong, H. Zhai and H. I. Maibach, *Skin Pharmacology and Physiology*, 2007, **20**, 272–282.
- 94 V. Goffin, F. Henry, C. Piéard-Franchimont and G. E. Piéard, *Skin Pharmacology and Physiology*, 2000, **13**, 280–284.
- 95 C. J. Martin, N. Alcock, S. Hiom and J. C. Birchall, *Pharmaceutics*, 2017, **3**, 31–49.
- 96 P. Karande, A. Jain, K. Ergun, V. Kispersky, S. Mitragotri and J. N. Israelachvili, *Proceedings of the National Academy of Sciences of the United States of America*, 2005, **102**, 4688–4693.
- 97 D. Bremseth and F. Pass, *Diabetes Technology & Therapeutics*, 2001, **3**, 225–232.
- 98 J. M. Spencer, *American Journal of Clinical Dermatology*, 2005, **6**, 89–92.
- 99 J. H. Park, J. W. Lee, Y. C. Kim and M. R. Prausnitz, *International Journal of Pharmaceutics*, 2008, **359**, 94–103.
- 100 W. R. Lee, S. C. Shen, H. H. Lai, C. H. Hu and J. Y. Fang, *Journal of Controlled Release*, 2001, **75**, 155–166.
- 101 A. Arora, M. R. Prausnitz and S. Mitragotri, *International Journal of Pharmaceutical Investigation*, 2008, **364**, 227–236.
- 102 J. Riviere and M. Heit, *Pharmaceutical Research*, 1997, **14**, 687–697.
- 103 M. R. Prausnitz, *Advanced Drug Delivery Reviews*, 1999, **35**, 61–76.
- 104 S. Mitragotri, *Journal of Controlled Release*, 2001, **71**, 23–29.
- 105 E. M. Migdadi, A. J. Courtenay, I. A. Tekko, M. T. C. McCrudden, M. C. Kearney, E. McAlister, H. O. McCarthy and R. F. Donnelly, *Journal of Controlled Release*, 2018, **285**, 142–151.
- 106 J. Y. Fang, K. C. Sung, O. Y. P. Hu and H. Y. Chen, *Arzneimittel-Forschung/Drug Research*, 2001, **51**, 408–413.
- 107 O. Pillai and R. Panchagnula, *Journal of Controlled Release*, 2003, **89**, 127–140.
- 108 T. A. Pereira, D. N. Ramos and R. F. V. Lopez, *Scientific Reports*, 2017, **7**, 1–10.
- 109 M. Pitorre, H. Gondé, C. Haury, M. Messous, J. Poilane, D. Boudaud, E. Kanber, G. A. Rossemmond Ndombina, J. P. Benoit and G. Bastiat, *Journal of Controlled Release*, 2017, **266**, 140–155.

- 110 S. B. Shirsand, M. S. Para, D. Nagendrakumar, K. M. Kanani and D. Keerthy, *Journal of Acute Disease*, 2012, **2**, 201–207.
- 111 C. Richard, E. Souloumiac, J. Jestin, M. Blanzat and S. Cassel, *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 2018, **558**, 373–383.
- 112 Z. Pavelic, N. Skalko-Basnet and R. Schubert, *International Journal of Pharmaceutics*, 2001, **219**, 139–149.
- 113 R. J. Laxmi, R. Karthikeyan, P. S. Babu and R. V. V. N. Babu, *Journal of Acute Disease*, 2013, **2**, 115–121.
- 114 P. N. Desai, Q. Yuan and H. Yang, *Biomacromolecules*, 2010, **11**, 666–673.
- 115 H. Yang, P. Tyagi, R. S. Kadam, C. A. Holden and U. B. Kompella, *ACS Nano*, 2012, **6**, 7595–7606.
- 116 V. Patel, H. Kukadiya, R. Mashru, N. Surti and S. Mandal, *Iranian Journal of Pharmaceutical Research*, 2010, **9**, 327–334.
- 117 M. A. Yamane, A. C. Williams and B. W. Barry, *International Journal of Pharmaceutics*, 1995, **116**, 237–251.
- 118 E. Tuitou, B. Godin, Y. Karl, S. Bujanover and Y. Becker, *Journal of Controlled Release*, 2002, **80**, 1–7.
- 119 H. Chen, X. Chang, D. Du, W. Liu, J. Liu, T. Weng, Y. Yang, H. Xu and X. Yang, *Journal of Controlled Release*, 2006, **110**, 296–306.
- 120 S. Peltola, P. Saarinen-Savolainen, J. Kiesvaara, T. M. Suhonen and A. Urtti, *International Journal of Pharmaceutics*, 2003, **254**, 99–107.
- 121 M. J. Lawrence and G. D. Rees, *Advanced Drug Delivery Reviews*, 2012, **64**, 175–193.
- 122 Ajazuddin, A. Alexander, A. Khichariya, S. Gupta, R. J. Patel, T. K. Giri and D. K. Tripathi, *Journal of Controlled Release*, 2013, **171**, 122–132.
- 123 A. Jain, P. Deveda, N. Vyas and J. Chauhan, *Int J Pharm Res Dev*, 2011, **2**, 18–25.
- 124 D. Mou, H. Chen, D. Du, C. Mao, J. Wan, H. Xu and X. Yang, *International Journal of Pharmaceutics*, 2008, **353**, 270–276.
- 125 H. Chen, X. Chang, D. Du, J. Li, H. Xu and X. Yang, *International Journal of Pharmaceutics*, 2006, **315**, 52–58.
- 126 H. Chen, D. Mou, D. Du, X. Chang, D. Zhu, J. Liu, H. Xu and X. Yang, *International Journal of Pharmaceutics*, 2007, **341**, 78–84.
- 127 C. Valenta and K. Schultz, *Journal of Controlled Release*, 2004, **95**, 257–265.
- 128 V. Sabale and S. Vora, *International Journal of Pharmaceutical Investigation*, 2012, **2**, 140.
- 129 M. Mohamed, *The AAPS Journal*, 2004, **6**, e26.
- 130 M. Shahin, S. Abdel Hady, M. Hammad and N. Mortada, *AAPS PharmSciTech*, 2011, **12**, 239–247.
- 131 R. Jebbawi, S. Fruchon, C.-O. Turrin, M. Blanzat and R. Poupot, *Pharmaceutics*, 2020, **12**, 1224–1237.
- 132 C. Puglia, A. Offerta, G. G. Tirendi, M. S. Tarico, S. Curreri, F. Bonina and R. E. Perrotta, *Drug Delivery*, 2016, **23**, 36–40.
- 133 R. H. Müller, M. Radtke and S. A. Wissing, *Advanced Drug Delivery Reviews*, 2002, **54**, 131–155.
- 134 F. Q. Hu, Y. Hong and H. Yuan, *International Journal of Pharmaceutics*, 2004, **273**, 29–35.
- 135 M. Trotta, R. Cavalli, M. E. Carlotti, L. Battaglia and F. Debernardi, *International Journal of Pharmaceutics*, 2005, **288**, 281–288.
- 136 R. H. Müller, K. Mäder and S. Gohla, *European Journal of Pharmaceutics and Biopharmaceutics*, 2000, **50**, 161–177.
- 137 M. Ricci, C. Puglia, F. Bonina, C. Di Giovanni, S. Giovagnoli and C. Rossi, *Journal of Pharmaceutical Sciences*, 2005, **94**, 1149–1159.
- 138 C. Puglia, P. Blasi, L. Rizza, A. Schoubben, F. Bonina, C. Rossi and M. Ricci, *International Journal of Pharmaceutics*, 2008, **357**, 295–304.
- 139 K. Mitri, R. Shegokar, S. Gohla, C. Anselmi and R. H. Müller, *International Journal of Pharmaceutics*, 2011, **414**, 267–275.
- 140 M. Argimón, M. Romero, P. Miranda, Á. W. Mombrú, I. Miraballes, P. Zimet and H. Pardo, *Journal of the Brazilian Chemical Society*, 2017, **28**, 1177–1184.
- 141 A. Lippacher, R. H. Müller and K. Mäder, *International Journal of Pharmaceutics*, 2000, **196**, 227–230.
- 142 Z. Mei, Q. Wu, S. Hu, X. Li and X. Yang, *Drug Development and Industrial Pharmacy*, 2005, **31**, 161–168.
- 143 P. Paolicelli, F. Corrente, S. Cesa, F. Cereto and M. A. Casadei, *Journal of Chemical and Pharmaceutical Research*, 2011, **3**, 410–421.
- 144 R. V. Contri, L. A. Frank, M. Kaiser, A. R. Pohlmann and S. S. Guterres, *International Journal of Nanomedicine*, 2014, **9**, 951–962.
- 145 K. Bhaskar, C. K. Mohan, M. Lingam, S. J. Mohan, V. Venkateswarlu, Y. M. Rao, K. Bhaskar, J. Anbu and V. Ravichandran, *Drug Development and Industrial Pharmacy*, 2009, **35**, 98–113.
- 146 M. Kurakula, O. A. A. Ahmed, U. A. Fahmy and T. A. Ahmed, *Journal of Liposome Research*, 2016, **26**, 288–296.
- 147 G. Mancini, L. M. D. Gonçalves, J. Marto, F. A. Carvalho, S. Simões, H. M. Ribeiro and A. J. Almeida, *Pharmaceutics*, 2021, **13**, 328.
- 148 D. Patel, S. Dasgupta, S. Dey, Y. Roja Ramani, S. Ray and B. Mazumder, *Scientia Pharmaceutica*, 2012, **80**, 749–764.
- 149 M. Joshi and V. Patravale, *Drug Development and Industrial Pharmacy*, 2006, **32**, 911–918.
- 150 M. Y. Levy, W. Schutze, C. Fuhrer and S. Benita, *Journal of Microencapsulation*, 1994, **11**, 79–92.
- 151 W. Mehnert and C. Schwartz, *J Microencapsulation*, 1999, **16**, 205–213.
- 152 B. Müeller, J. Lucks, B. Stampa and R. Müeller, *Pharmazeutische Industrie*, 1990, **52**, 789–793.
- 153 C. Freitas and R. Müeller, *J Microencapsulation*, 1999, **16**, 59–71.
- 154 E. B. Souto, S. A. Wissing, C. M. Barbosa and R. H. Müller, *European Journal of Pharmaceutics and Biopharmaceutics*, 2004, **58**, 83–90.
- 155 M. J. Abla, N. D. Singh and A. K. Banga, eds. N. Dragicevic and H. I. Maibach, Springer Berlin Heidelberg, Berlin, Heidelberg, 2016, pp. 1–13.
- 156 K. Raza, B. Singh, S. Lohan, G. Sharma, P. Negi, Y. Yachha and O. P. Katore, *International journal of pharmaceutics*, 2013, **456**, 65–72.
- 157 M. Kirjavainen, A. Urtti, I. Jääskeläinen, T. Marjukka Suhonen, P. Paronen, R. Valjakka-Koskela, J. Kiesvaara and J. Mönkkönen, *Biochimica et Biophysica Acta - Lipids and Lipid Metabolism*, 1996, **1304**, 179–189.
- 158 E. Tuitou, N. Dayan and E. Tuitou, 2015, **21**, 1879–1885.
- 159 G. M. M. EL MAGHRABY, A. C. WILLIAMS and B. W. BARRY, *Journal of Pharmacy and Pharmacology*, 1999, **51**, 1123–1134.
- 160 P. L. Honeywell-Nguyen, S. Arenja and J. A. Bouwstra, *Pharmaceutical Research*, 2003, **20**, 1619–1625.
- 161 M. J. Choi and H. I. Maibach, *Skin Pharmacology and Physiology*, 2005, **18**, 209–219.
- 162 H. Schreier and J. Bouwstra, *Journal of Controlled Release*, 1994, **30**, 1–15.
- 163 I. P. Kaur, A. Garg, A. K. Singla and D. Aggarwal, *International Journal of Pharmaceutics*, 2004, **269**, 1–14.
- 164 T. G. Singh and N. Sharma, ed. A. M. B. T.-N. in G. F. and C. Grumezescu, William Andrew Publishing, 2016, pp. 149–174.
- 165 C. Mauroy, P. Castagnos, J. Orio, M. C. Blache, I. Rico-Lattes, J. Teissié, M. P. Rols and M. Blanzat, *Molecular Pharmaceutics*, 2015, **12**, 103–110.

- 166 J. Guo, Q. Ping, G. Sun and C. Jiao, *International Journal of Pharmaceutics*, 2000, **194**, 201–207.
- 167 D. B. G and V. L. P, *Future Journal of Pharmaceutical Sciences*, 2020, **6**, 100.
- 168 A. K. Seth, A. Misra and D. Umrigar, *Pharmaceutical Development and Technology*, 2004, **9**, 277–289.
- 169 C. C. Chang, W. Te Yang, S. Y. Ko and Y. C. Hsu, *Digest Journal of Nanomaterials and Biostructures*, 2012, **7**, 59–71.
- 170 D. G. Fatouros and S. G. Antimisiaris, *Journal of Colloid and Interface Science*, 2002, **277**, 271–277.
- 171 H. Hofland, J. Bouwstra, H. HE, Boddé, F. Spies and H. Junginger, *The British Journal of Dermatology.*, 1995, **132**, 853–866.
- 172 M. N. Azmin, A. T. Florence, R. M. Handjani-Vila, J. F. B. Stuart, G. Vanlerberghe and J. S. Whittaker, *Journal of Pharmacy and Pharmacology*, 1985, **37**, 237–242.
- 173 G. M. El Maghraby, B. W. Barry and A. C. Williams, *European Journal of Pharmaceutical Sciences*, 2008, **34**, 203–222.
- 174 S. Li, S. Li, Y. Q. Qiu, S. H. Zhang and Y. H. Gao, *Skin Pharmacology and Physiology*, 2012, **25**, 257–268.
- 175 İ. Eroğlu, E. Azizoğlu, M. Özyazıcı, M. Nenni, H. Güner Orhan, S. Özbal, İ. Tekmen, İ. Ertam, İ. Ünal and Ö. Özer, *Drug Delivery*, 2016, **23**, 1502–1513.
- 176 M. Manconi, J. Pendás, N. Ledón, T. Moreira, C. Sinico, L. Saso and A. Fadda, *The Journal of pharmacy and pharmacology*, 2009, **61**, 423–430.
- 177 P. Lakshmi, G. Devi, S. Bhaskaran and S. Sacchidanand, *Indian journal of dermatology, venereology and leprology*, 2007, **73**, 157–161.
- 178 G. Cevc, D. Gebauer, J. Stieber, A. Schätzlein and G. Blume, *Biochimica et Biophysica Acta - Biomembranes*, 1998, **1368**, 201–215.
- 179 A. Gupta, G. Aggarwal, S. Singla and R. Arora, *Scientia Pharmaceutica*, 2012, **80**, 1061–1080.
- 180 L. Boulmedarat, J. L. Grossiord, E. Fattal and A. Bochot, *International Journal of Pharmaceutics*, 2003, **254**, 59–64.
- 181 G. Leclair, P. Hildgen, A. Gupta and J. Leroux, *Journal of Controlled Release*, 2002, **82**, 373–383.
- 182 S. Mourtas, S. Fotopoulou, S. Duraj, V. Sfika, C. Tsakiroglou and S. G. Antimisiaris, *Colloids and Surfaces B: Biointerfaces*, 2007, **55**, 212–221.
- 183 S. Mourtas, M. Haikou, M. Theodoropoulou, C. Tsakiroglou and S. G. Antimisiaris, *Colloid and interface science*, 2008, **317**, 611–619.
- 184 C. Richard, E. Souloumiac, J. Jestin, M. Blanzat and S. Cassel, *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 2018, **558**, 373–383.
- 185 P. Khazaeli, A. Pardakhty and H. Shoorabi, *Drug Delivery*, 2007, **14**, 447–452.
- 186 Ž. Pavelić, N. Škalko-Basnet, J. Filipović-Grčić, A. Martinac and I. Jalšenjak, *Journal of Controlled Release*, 2005, **106**, 34–43.
- 187 Ž. Pavelić, N. Škalko-Basnet and I. Jalšenjak, *International Journal of Pharmaceutics*, 2005, **301**, 140–148.
- 188 K. Letchford and H. Burt, *European Journal of Pharmaceutics and Biopharmaceutics*, 2007, **65**, 259–269.
- 189 T. J. de Faria, A. Machado de Campos and E. Lemos Senna, *Macromolecular Symposia*, 2005, **229**, 228–233.
- 190 S. S. Guterres, M. P. Alves and A. R. Pohlmann, *Drug Target Insights*, 2007, **2**, 117739280700200.
- 191 R. Alvarez-Román, G. Barré, R. H. Guya and H. Fessi, *European Journal of Pharmaceutics and Biopharmaceutics*, 2001, **52**, 191–195.
- 192 E. Soussan, S. Cassel, M. Blanzat and I. Rico-Lattes, *Angewandte Chemie - International Edition*, 2009, **48**, 274–288.
- 193 D. Huang, M. Sun, Y. Bu, F. Luo, C. Lin, Z. Lin, Z. Weng, F. Yang and D. Wu, *Journal of Materials Chemistry B*, 2019, **7**, 2330–2337.
- 194 Q. Zeng, Y. Qian, Y. Huang, F. Ding, X. Qi and J. Shen, *Bioactive Materials*, 2021, **6**, 2647–2657.
- 195 S. A. Bernal-Chávez, S. Alcalá-Alcalá, D. Cerecedo and A. Ganem-Rondero, *European Journal of Pharmaceutical Sciences*, 2020, **146**, 105231.
- 196 Z. Wang, X. Liu, Y. Duan and Y. Huang, *Mol. Pharmaceutics*, 2021, **18**, 4099–4110.
- 197 H. Jung, M. K. Kim, J. Y. Lee, S. W. Choi and J. Kim, *Advanced Functional Materials*, 2020, **30**, 2004407.
- 198 D. Nunes, S. Andrade, M. J. Ramalho, J. A. Loureiro and M. C. Pereira, *Polymers*, 2022, **14**, 1010.
- 199 M. Wang, S. K. Marepally, P. K. Vemula and C. Xu, in *Nanoscience in Dermatology*, eds. M. R. Hamblin, P. Avci and T. W. Prow, Academic Press, Boston, 2016, pp. 57–72.