

REVIEW ARTICLE

Recent advances in gel technologies for topical and transdermal drug delivery

Khurram Rehman and Mohd Hanif Zulfakar

Centre for Drug Delivery Research, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Abstract

Transdermal drug delivery systems are a constant source of interest because of the benefits that they afford in overcoming many drawbacks associated with other modes of drug delivery (i.e. oral, intravenous). Because of the impermeable nature of the skin, designing a suitable drug delivery vehicle that penetrates the skin barrier is challenging. Gels are semisolid formulations, which have an external solvent phase, may be hydrophobic or hydrophilic in nature, and are immobilized within the spaces of a three-dimensional network structure. Gels have a broad range of applications in food, cosmetics, biotechnology, pharmatechnology, etc. Typically, gels can be distinguished according to the nature of the liquid phase, for example, organogels (oleogels) contain an organic solvent, and hydrogels contain water. Recent studies have reported other types of gels for dermal drug application, such as proniosomal gels, emulgels, bigels and aerogels. This review aims to introduce the latest trends in transdermal drug delivery via traditional hydrogels and organogels and to provide insight into the latest gel types (proniosomal gels, emulgels, bigels and aerogels) as well as recent technologies for topical and transdermal drug delivery.

Keywords

Aerogels, bigels, emulgels, hydrogels, niosomes, oleogels, topical, transdermal drug delivery

History

Received 15 March 2013
Revised 5 July 2013
Accepted 11 July 2013
Published online 13 August 2013

Introduction

The skin is the human body's largest organ. It covers the entire body and serves as a line of defense against the external invasion of microorganisms and other environmental stressors such as heat, entry of chemicals and toxins, as well as dehydration¹. Since the skin is the organ that is most exposed to the environment, the risk of damage of its integrity or the occurrence of a localized disease is very high. Transdermal drug delivery via the skin is beneficial, because it avoids the risks associated with intravenous therapy and the inconveniences associated with varying gastric pH, emptying time, and hepatic metabolism. Transdermal administration of drugs is not easy because of the impermeable nature of the skin. The stratum corneum, which varies from ten to several hundred micrometers in thickness, provides the first line of defense as a "permeability barrier", not allowing macromolecules to easily pass through the dermal layer². The stratum corneum consists of layers of dead keratinocytes which are surrounded by a lipid matrix, similar to a "brick and mortar system", which makes it difficult for drug molecules to pass through the skin^{3,4}. Although recent advancements in nanotechnology have enhanced the ability of molecules to pass through the skin by improving the pharmacokinetics of drugs; however, an appropriate vehicle

remains to be developed to ensure drug delivery using noninvasive techniques.

The gels can prove to be a beneficial vehicle for topical drug delivery or for the localized drug action on skin such as in case of sprains or acute musculoskeletal disorders. A gel is defined as a semisolid formulation, which exhibits an external solvent phase, is hydrophobic or hydrophilic in nature, and is immobilized within the spaces available of a three-dimensional network structure. Gels are unique materials that are rigid and elastic in nature⁵ and have a broad range of applications in cosmetics, medicine, biomaterials and food technologies^{6–8}. Moreover, gels principally consist of a fluid solvent with the minority component being a solid matrix⁹. In general, a gelling agent such as a carbomer or a natural gum (i.e. xanthan gum) is dispersed in purified water to form a uniform dispersion. Compared to creams and ointments, gels, because of their high water content, permit a greater dissolution of drugs and facilitate migration of the drug through the vesicle. In addition, gels can hydrate the skin by retaining a significant amount of transepidermal water and facilitate drug transport¹⁰.

Typically, gels may be differentiated into two different types according to the nature of their liquid phase. For example, organogels (oleogels) contain an organic solvent and hydrogels contain water. In recent studies, additional types of gels have been reported for dermal application of a drug, such as proniosomal gels, emulgels, bigels and aerogels (Table 1). This study aimed to introduce the latest trends and terminologies of gel systems (i.e. proniosome gels, emulgels, bigels and aerogels) in topical drug delivery on skin.

Address for correspondence: Mohd Hanif Zulfakar, PhD, Centre for Drug Delivery Research, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia. Tel: +6 03 92897971. Fax: +6 03 26983271. E-mail: hanif@pharmacy.ukm.my

Table 1. Gel Types and their distinguishing features and examples of commercial products.

Gel Type	Distinguishing features	Commercial product®	Indication
Hydrogels	Water entrapped in a three-dimensional network by using a hydrophilic gelling agent	Atopro, Aurstat, Nimulid Transgel, Luofucon, Tegaderm, Skinintegrity, Maxgel	Atopic dermatitis Eczema Anti-inflammatory Skin care
Oleogels/ Organogels	Organic liquid entrapped in a three-dimensional network by using an organogelator	Oleogel Plus, Gilugel, Phlojel Ultra, Eucerin, Circularom, Przondo, Lancamento	Skin Care Emollient Compounding base
Niosomal and Proniosomal gels	Liposomes consisting of a nonionic surfactant, which can be of a hydrogel or oleogel nature. A proniosomal gel is a hydrated form of niosomes.	Premiere Massage gel, Lancome niosome plus	Skin care Cosmetic antiaging
Emulgels	Consist of a hydrogel or oleogel with o/w or w/o emulsion and a surfactant	Voltaren, Voveran, Voltarol, Biogel, White glow, Topicane	Anti-inflammatory Skin care
Bigels	Mixture of an oleogel and hydrogel without the addition of a surfactant	Bi-Gel Testosterone	Anti-inflammatory (Clinical stage)
Aerogels and Xerogels	Inorganic, composed of silica, and produced by supercritical drying. Inorganic, composed of silica, produced by drying under normal pressure	Aerosil (only patented prototypes)	No pharmaceutical commercial product for topical

Hydrogels

Gels that consist of an aqueous dispersion medium that is gelled with a suitable hydrophilic gelling agent are known as hydrogels. Hydrogels are three-dimensional hydrophilic polymer networks, which have the ability to absorb large quantities of water¹¹. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), carbapol and sodium alginate have been previously investigated as gelling agents^{12,13}. Hydrogels can be formed via chemical or physical crosslinks, which provide a networked structure and physical stability. These physical crosslinks include entanglements, crystallites, Van der Waals interactions or hydrogen bonding. Hydrogels formed from physical crosslinks are known as ‘reversible’ or ‘physical’ hydrogels^{9,14}. In contrast, hydrogels known as ‘chemical’ or ‘permanent’ gels are formed via covalently bonded crosslinked networks^{6,8}.

Drug release from hydrogels can occur from different mechanisms: diffusion and by chemical stimulation. Diffusion is regulated by movement through the polymer matrix or by bulk erosion of the hydrogel. Chemical stimulated gels swell in response to external cues like pH and temperature or by enzymatic action¹⁵ and effectively open their pores for release of the entrapped drug. This type of mechanism can be used for targeted drug release only for diseased tissues. Drug release via diffusion is more common for localized and non specific drug release whereas drug release by chemical stimulation have seen its more application for oral drug delivery and can offer control for selective treatment^{11,16}.

Recently, advances in hydrogel technologies have increased the application of hydrogels in biomedical sciences, i.e. in cell encapsulation, tissue repair and in controlled drug delivery. Many novel hydrogel-based delivery matrices have been designed and fabricated to fulfill the increasing needs of pharmaceutical and medical fields^{17,18}. Moreover, hydrogels based on acrylated poloxamine have been investigated for the purpose of drug delivery and tissue engineering¹⁹. Investigation of poloxaminehydrogels²⁰ and polymerized oligolactides²¹ as a delivery vehicle for hydrophobic drugs and bioactive molecules is a current trend in gel technology. Furthermore, chitosan hydrogels have been

studied as potential candidate vehicles for localized drug delivery of drugs with challenges in bioavailability because of poor solubility after oral absorption¹⁶. Moreover, chitosan hydrogels have been examined for their use in the delivery of berberine alkaloid and active *s*-enantiomer of racemic propranolol²². Nanotechnology has played a vital role in the transdermal drug delivery of molecules using hydrogels, such as heparin, which cannot easily penetrate the skin^{23,24}. Wound healing and anti-scar activity have been extensively studied and still is the area of focus among the researchers. Many therapeutic agents such as astragaloside IV²⁵, curcumin²⁶ and triamcinolone acetonid, have been loaded in hydrogels for the purpose of efficient wound healing²⁷. The astragaloside IV-based hydrogels exhibited angiogenic effects on wound repair and inhibitory efficacy on scar complication. It also contributed collagen organization, by maintaining type III/type I collagen ratio, in adult tissues resulting into anti-scar activity²⁵. A thermosensitive hydrogel of curcumin-loaded micelles was prepared to enhance the cutaneous wound healing process. It was suggested that the combination of bioactivity of curcumin and thermosensitive hydrogel promoted tissue reconstruction processes and has a potential for cutaneous wound healing²⁶. Some of the advantages and drawbacks of hydrogels are described in Table 2.

Organogels

Gels containing oil or non-polar liquids as a dispersion medium are known as organogels (also called oleogels). Organogels are defined as organic liquid entrapped within a thermoreversible three-dimensional gel network. Organogels are solid-like systems based on the gelatin of organic solvents via low-molecular-weight components or oil-soluble polymers that produce a three-dimensional network, which entraps a liquid solvent known as organogelators^{28–30}. The formation of organogels is similar to that of hydrogels, which contain weak interactions such as Van der Waals forces or hydrogen bonding^{31,32}. Many organic solvents such as benzene and hexane²⁸, edible oils such as sweet almond oil, cod liver oil, and olive oil (as a liquid phase)^{30,33,34}, and many waxes, including candelilla wax, rice bran wax, carnauba wax, and

Table 2. Advantages and drawbacks of hydrogels.

Advantages	Drawbacks
Can be easily prepared	Mechanical strength may be an issue in hydrogels
Less expensive	Transdermal drug delivery can be problematic because of its hydrophilic nature
Biodegradable	Lipophilic compounds are not easy to incorporate into hydrogels
Versatile, many compounds can be incorporated	Microbial contamination can occur in polysaccharide-based hydrogels
Primary foundation of many other gel forms such as liposomal gels, emulgels and bigels	

Table 3. Advantages and drawbacks of organogels.

Advantages	Drawbacks
Ease of preparation	More favorable towards lipophilic drugs
Less expensive	Heat can be an issue for stability unless specific ingredients such as lecithin are added
Shows increased mechanical strength because of the organogelator	Oily texture can be an unpleasant feature for cosmetics
Higher permeability through the skin	Not easily washable
Thermoreversible	
Resistant to microbial contamination	

sugarcane wax^{35,36} have been investigated for their use as organogelators in the development of a vehicle for the transdermal drug delivery of lipophilic compounds^{37,38}. Increased interest for organogels may be because of the ability of organogelators to form a crystalline network and entrap bulk oils despite low concentrations (<10% wt). Organogels provide a proper texture and stabilize many heterogeneous systems^{28,39}. In addition to the ease of preparation, organogels can enhance drug penetration through the stratum corneum because of their lipophilic nature. Many typical organogel components are known as permeation enhancers such as fatty acids, surfactants, glycols, essential oils and terpenes. Many fatty acids moieties are termed as penetration enhancers, because they are thought to create separate domains, which are highly permeable pathways and helps into penetration of fatty acids into lipid bilayer of stratum corneum. Components like surfactants and phospholipids absorb into the stratum corneum and increase tissue hydration, consequently increasing drug permeation, especially in the case of hydrophilic active agents^{7,40}. In addition, the oils used in organogels are safe for the formulation of drug delivery systems of lipophilic compounds³⁸.

Recently, lecithin organogels (phospholipids obtained from egg yolks) have attracted attention for the transdermal delivery of drugs because of their ability to solubilize substances with different physicochemical properties, and their biocompatibility^{7,41–43}, thermodynamic stability, thermoreversible nature, resistance to microbial contamination, and insensitivity to moisture. As the lecithin itself provides skin protection against UV-induced skin aging, it shows additive effects along with incorporated bioactive agents against skin aging. A wide variety of guest molecules such as vitamins A and C, hormones, NSAIDs, peptides, amino acids, local anesthetics and antifungal agents were reported to be effective topically as well as transdermally when delivered by Lecithin organogels^{41–44}. Several advantages and drawbacks of organogels are described in Table 3.

Niosomes and proniosome gels

Niosomes are liposomes consisting of a nonionic surfactant. They may be either unilamellar or multilamellar vesicles that are capable of carrying both hydrophilic and hydrophobic drugs. The chemical stability of niosomes is greater than that of phospholipid

vesicles^{45,46}. Proniosomes are liquid crystalline compact niosomal hybrids, which may be converted into niosomes upon hydration⁴⁷. Vesicular drug delivery systems are capable of encapsulating the drug and can enhance bioavailability, therapeutic activity and permeation properties^{48–50}. These gels can be primarily formulated by either hydrogels or organogels. Organogel-based niosomal gels have been investigated as carriers of liposoluble vitamins⁵¹ and as a delivery vehicle for antigens⁵²; however, hydrogel niosomes and proniosomes have been studied more extensively as potential carriers for transdermal drug delivery⁵³. The combination of hydrogels and niosomes improves the controlled release of drugs in the treatment of dermal diseases⁴⁶. Niosomes, which are prepared using a film hydration technique, consist of a lipid film that is prepared and then hydrated under mechanical stirring, and the large unilamellar vesicles are prepared using an extrusion technique^{54,55}. In addition, the ability of niosomes to function as penetration enhancers for the passing of drug molecules through the skin, and their biodegradable and nontoxic properties have attracted considerable interest in topical and transdermal drug delivery technology. Nonionic surfactant vesicles (niosomes) have also been studied because of their several advantages over liposomes with regard to their higher chemical stability, intrinsic skin penetration-enhancing properties, and lower costs of production^{56–58}. Although liposomes can encapsulate a wide variety of drugs and can deliver these drugs to target sites, liposomes have a high cost with a short shelf-life because of their phospholipid composition, which may be hydrolyzed⁵⁹. Nonionic surfactants (i.e. Span and Tween 60) may be used as substitutes for phospholipids in the formation of bilayer vesicles because they are less expensive and show a higher chemical stability compared to phospholipids^{56,60,61}. These niosomes are then incorporated into hydrogels or organogels by gentle stirring to form niosomal gels.

Proniosomal hydrogels have also been characterized for their potential use as transdermal drug delivery vehicles^{62,63}. Proniosomes are also known as “dry niosomes” because they require hydration to form niosomal vessels before drug release and permeation through the skin⁴⁷. Unlike niosomes, proniosomes are not separately prepared; however, all of the preparation steps such as the addition of a surfactant and a gelling agent is simultaneously performed and they are dispersed in a warm water bath. Subsequently, the dispersion is cooled down at room

Table 4. Advantages and drawbacks of niosomal and proniosomal gels.

Advantages	Drawbacks
Compared to liposomes, niosomes offer greater stability and proniosomes are more stable than niosomes Simple preparation method Greater skin permeability Suitable for both lipophilic and hydrophilic drugs	Niosomes aggregate, sediment, and degrade via hydrolysis and fusion Expensive

Table 5. Advantages and drawbacks of emulgels.

Advantages	Disadvantages
Ease of preparation and low preparation cost Thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, water-soluble, long shelf life, bio-friendly, transparent and pleasing appearance Emulgels can be used in the controlled release of drugs	Occurrence of bubbles during emulgel preparation Presence of the surfactant can cause skin irritation

temperature until it is converted into a proniosomal gel⁵⁷. Moreover, proniosomes are hydrated by agitation in hot water and provide a unique vesicle with the potential –for transdermal drug delivery⁶³. In addition, proniosomal hydrogels are considered to be more effective than niosomal hydrogels because the former can overcome many physical stability problems (i.e. aggregation, sedimentation, degradation by hydrolysis and fusion) that are associated with niosomes⁶⁴. Furthermore, proniosomal gels may also be more effective in transdermal drug delivery because they enhance the drug permeation from the skin barrier⁶⁵. Niosomes are capable of diffusing across stratum corneum as a whole; apart from this niosomes can interact with stratum corneum and adhere to the cell surface which causes a high thermodynamic activity gradient of the drug at the vesicle-stratum corneum surface, results in the driving force for the penetration of lipophilic drugs across the stratum corneum^{56,58}. Niosomes may also modify stratum corneum structure which makes the inter-cellular lipid barrier of stratum corneum looser and more permeable^{48,57–59,65}. Niosomes are very beneficial vesicular system for topical and transdermal delivery because they act as a reservoir of drug for a prolonged period of time and enhance skin penetration, as studied in estradiol loaded niosomes made with the inclusion of cholesterol facilitated estradiol transdermal permeation⁵⁷. Some of the advantages and drawbacks of niosomal and proniosomal gels are described in Table 4.

Emulgels

An emulgel is a combination of an emulsion and a gel. Although gels have many advantages, the delivery of hydrophobic drugs has consistently been a point of concern. To overcome this limitation, emulgels were introduced^{66,67} and have been used for hydrophobic drug delivery. The presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. Both water-in-oil (w/o) and oil-in-water (o/w) emulsions have been used as a vehicle to deliver drugs. Emulgels have several favorable dermatological properties such as thixotrophicity, greaselessness, spreadability, removability, emollient, long shelf-life and a pleasing appearance^{68–70}. In addition, emulgels have a high patient acceptability because they possess the combined advantages of both emulsions and gels. Emulgel formulations prepared from carbopol and HPMC have optical clarity, are easy to prepare, and have high diffusion and absorption rates⁷¹. Microemulsions reduce the diffusion barrier of the stratum corneum^{72,73} and show acceptable physical properties, drug release and low skin irritation^{68,74,75}. In addition, emulgels have shown their potential as an excellent vehicle for skin care products for protection

against ultraviolet A and B (UVA/UVB radiation)⁷⁶. Recently, microemulsion-based gels (MBGs) have generated great interest as a potential topical drug delivery vehicle on skin^{77–83}. These gels can be classified as emulgels since they consist of emulsions (oil and surfactant), but their particle size is reduced, thereby making them more stable than emulgels. A gelling agent is dissolved in hot w/o or o/w microemulsion and then cooled down, which causes gelatin. The advantages associated with micro-emulsions include their thermodynamic stability. Thus, micro-emulsion-based gels may be a promising vehicle for topical transdermal drug delivery. In addition, MBGs containing carbopol and xanthan gum as gelling agents, and PEG-8 capric glycerides and polyglyceryl-6 dioleate as surfactants, have been investigated for topical drug delivery on the skin^{72,84}. Lecithin-containing microemulsion organogels based on either cyclohexane or iso-octane have been reported to enhance permeability rates through the excised human skin by 10-fold compared to control solvents⁴⁴. In addition, microemulsion-based organogels can be prepared using a variety of pharmaceutically acceptable surfactants and oils, including Tween 80 and 20 and isopropyl myristate^{85,86}. MBGs have percolative electroconductive channels and can be used to solubilize hydrophilic drugs and vaccines as well as hydrophobic materials in the continuous oil phase⁷¹. Nanotechnology has also been introduced in emulsion-based gels, thereby reducing their particle size into nano-sizes and increasing stability and skin penetration⁸⁵. The drug passage through the stratum corneum in emulgels and microemulsion gels is based on conventional diffusion mechanism, but the surfactants and the fatty acids in oil phase, may also act as penetration enhancers and can cause the increased drug penetration and accumulation into the skin. Some of the advantages and drawbacks of emulgels are described in Table 5.

Bigels or bi (phasic) gels

Bigels are topical formulations that are obtained by combining an aqueous (hydrogels) and lipophilic (organogels) system. Bigel formulations possess characteristics of both gels such as the cooling effect, enhancement of hydration of the stratum corneum, moisturizing effect, easily spreadable, emollients and water-washability upon application to the skin. Bigels are stable oleogel and hydrogel mixtures that are devoid of any surfactant or emulsion stabilizer⁸⁷. These homogenous preparations are prepared by mixing aqueous and lipophilic systems at a high shear rate or rpm. Since there is no surfactant or emulsifier, bigels differ from creams and emulgels in terms of formulation. The use of two gel systems in bigels can produce a synergetic effect such

Table 6. Advantages and drawbacks of bi (phasic) gels.

Advantages	Drawbacks
Synergistic effect of hydrogels and oleogels	Difficulty in controlling phase separation since there is no emulsifying agent present
Ease of preparation	Not extensively studied
No emulsifier	Not thermo-reversible since stability can be issue at higher temperatures
No surfactant induced skin irritation	
Can deliver lipophilic and hydrophilic drugs through the skin	

as enhancement of hydration of stratum corneum, and drug penetration due to presence of both water phase and oil phase⁸⁸. The mechanism of action of drug penetration through skin will be of same nature as of hydrogels and oleogels. The conventional diffusion of hydrogels and lipophilic nature of oils along with fatty acids as penetration enhancers will able the drug to pass through stratum corneum and produce the topical and transdermal effect on skin. Because bigels possess the combined features and advantages of organogels and hydrogels, they may potentially be used as a topical drug delivery vehicle on skin in the pharmaceutical and cosmetic industries. Carbopol hydrogels and oleogels obtained from sweet almond oil and liquid paraffin have been studied for the purpose of forming bigels⁸⁸. Unlike other multiphase systems, these bigels do not require the addition of emulsifiers or surfactant to achieve physical stability, but still it remains unclear that how the bigels will behave under longer duration and different storage conditions. Syneresis is an indicator of the formulation's lifetime, and in an ordinary gel, it is thought to result from the contraction of a solid network of tubules, resulting in the fluid being pushed out and separation of the two phases of the gel system. Syneresis is thought to more likely occur in bigels consisting of larger aggregates⁸⁹. Although bigels are very easy to prepare, few studies have evaluated these vehicles for pharmaceutical or cosmetic purposes. This may be due to the difficulty in obtaining a stable hydrogel and oleogel mixture without the addition of an emulsifier or a surfactant, and it may demonstrate specific drawbacks as discussed in Table 6.

Aerogels and xerogels

Aerogels and xerogels are also known as inorganic gels, since both types of gels are composed of silica. Both aerogels and xerogels have been investigated for their potential use as drug delivery vehicles⁹⁰. Silica xerogels have been studied in controlled subcutaneous drug delivery⁹¹. Silica xerogels have been evaluated as drug delivery implants and demonstrate potential as a drug delivery device or disc⁹². In contrast, silica aerogels have been investigated for dermal drug delivery; however, further characterization and investigation are needed to evaluate their potential.

Both aerogels and xerogels consist of silica, and both gels are created by a sol-gel process, although they undergo different drying procedures. If a wet silica gel is dried at normal pressure, it significantly shrinks and results in a dense material with a relatively small pore size, which is known as a xerogel. In supercritical drying, shrinkage is avoided and the unusually porous structure is preserved in the resulting aerogel. Aerogels are more flexible in terms of their structure, and their pore size and surface area can be customized⁹³. Furthermore, aerogels are considered more effective than xerogels because their drug solubility and bioavailability can be controlled by manipulating their release kinetics with the addition of different functional groups⁹¹. Differences between aerogels and xerogels are briefly described in Table 7.

Table 7. Differences between aerogels and xerogels.

Property	Aerogel	Xerogel
Composition	Silica	Silica
Bulk Density	0.003–0.35 g/cm ³	0.25–0.6 g/cm ³
Inner surface	400–1000 m ² /g	300–600 m ² /g
Pores	Larger pores	Smaller pores
Manufacturing	Sol-gel process	Sol-gel process
Drying	Supercritical drying	Dried at normal pressure

Hydrophilic aerogels can result in an extremely fast release of drugs, which is particularly advantageous for poorly water-soluble drugs⁹⁴. This effect is based on the collapse of the hydrophilic aerogel structure in aqueous solutions due to the surface tension inside the pores. Unlike aerogels, xerogels do not demonstrate a collapse in structure. Hydrophilic silica aerogels represent a new opportunity for dermal drug delivery. The drug loading procedure (adsorption from supercritical gases) allows for homogeneous distribution of the drug inside the aerogel matrix at a molecular level, so that the drugs are present inside the highly porous matrix in a non-crystalline form. It has been reported that a drug-loaded aerogel matrix can improve the drug release and penetration properties of semisolid formulations as well as stability⁹¹.

Although silica aerogels have been shown to be a potential drug delivery vehicle, they are not biodegradable, which limits their use. Several attempts have been made to produce biodegradable aerogels by using polysaccharides to overcome the drawback of nonbiodegradability in silica aerogels^{92,95–97}, and to produce a drug carrier in a dry form that is susceptible to charges with high loadings of an active compound⁹⁸. Polysaccharide-based aerogels as carriers have shown great potential as a drug carrier using hybrid aerogels consisting of inorganic and organic (polysaccharide) components. The individual coating of aerogel particles with biodegradable polymers by using spout-fluidized bed technology has been reported as a technological solution to overcome the premature release of a drug from the matrix before it reaches the target site⁹⁵. The use of these dissimilar components in a single aerogel matrix will result in novel and outstanding physicochemical properties of the aerogel. The preparation of aerogels for tissue engineering from polysaccharides (chitosan) has been recently reported⁹⁹. Alginate-multi-membrane aerogels were prepared for prolonged release of drug. It was concluded that the ratio of drug loading could be increased and the duration of drug release could be prolonged with the increase in number of alginate membranes. The resulting extended-release products could offer some potential advantages during patient compliance, and therapeutic outcomes¹⁰⁰. Some of the advantages and drawbacks of aerogels and xerogels are described in Table 8. Engineering of the drug release profile via coating of aerogel-based particles for targeted drug delivery systems will provide insight into its value to a product. However, the development of drug delivery technology systems consisting of aerogel coatings

Table 8. Advantages and drawbacks of aerogels and xerogels.

Advantages	Disadvantages
Aerogels can be customized (unlike xerogels) for prolonged drug delivery Highly stable Low thermal conductivity and thermally stable Large surface area for drug carrying Both aerogels and xerogels can be used for controlled drug delivery	Expensive technique Problems with biodegradation of pure silica aerogels and xerogels

with a precise control over layer thickness whilst avoiding aerogel structure collapse remains a challenge.

Conclusion

Gels have consistently been studied for their role in topical and transdermal drug delivery and recent developments in pharmaceutical science and technology have not only improved conventional gels, e.g. hydrogels as drug delivery system, but also introduced new variations of semisolid vehicles particularly for transdermal delivery such as proniosomes and microemulsion gels (MBGs) gels. These new developments in gel technologies are effective in delivering the drug across the skin but still there are many drawbacks which are yet to be addressed. More insight in bigels and aerogels may lead to new breakthrough for feasible topical and transdermal drug delivery. Further studies in gel technologies will prove to be beneficial in overcoming the drawbacks of each gel system and for developing a cost effective delivery systems for pharmaceutical and cosmetics application.

Declaration of interest

The writers have shown no conflict of interest.

The authors would like to thank the Center for Research and Instrumentation, and the Faculty of Pharmacy, Universiti Kebangsaan Malaysia in providing research grant under the code UKM-GUP-2011-016 and support during our studies.

References

- Lukas L. The epidermal permeability barrier. *Anat Embryol* 1988; 178:1–13.
- Peter ME. Structure and function of the stratum corneum permeability barrier. *Drug Develop Res* 1988;13:97–105.
- Michaels A, Chandrasekaran S, Shaw J. Drug permeation through human skin: theory and *in vitro* experimental measurement. *AIChE* 1975;21:958–96.
- Kiyomi W, Takuya H, Kenjiro Y, et al. An insight into the role of barrier related skin proteins. *Int J Pharm* 2012;427:293–8.
- Abdallah DJ, Weiss RG. Organogels and low molecular mass organic gelators. *Adv Mater* 2000;12:1237–47.
- Allan SH. Hydrogels for biomedical applications. *Adv Drug Deliv Rev* 2012;64:18–23.
- Vintiloiu A, Leroux JC. Organogels and their use in drug delivery – a review. *J Control Release* 2008;125:179–92.
- Otto W, Drahoslav L. Hydrophilic gels in biologic use. *Nature* 1960; 185:117–18.
- Shapiro YE. Structure and dynamics of hydrogels and organogels: an NMR spectroscopy approach. *Prog Polym Sci* 2011;36: 1184–253.
- Chang RK, Raw A, Lionberger R, Yu L. Generic development of topical dermatologic products: formulation development, process development, and testing of topical dermatologic products. *AAPS J* 2013;15:41–52.
- Peppas NA, Bures P, Leobandung W, Ichikawa H. Hydrogels in pharmaceutical formulation. *Eur J Pharm Biopharm* 2000;50:27–46.
- Gupta A, Mishra AK, Singh AK, et al. Formulation and evaluation of topical gel of diclofenac sodium using different polymers. *Drug Invention Today* 2010;5:250–3.
- Martinez RMA, Julian LVG, Maria MdB, et al. Rheological behavior of gels and meloxicam release. *Int J Pharm* 2007;333: 17–23.
- Davide C, Patrick D, Marco R, et al. Semisynthetic resorbable materials from hyaluronan esterification. *Biomaterial* 1998;19: 2101–27.
- Mohd CIMA, Naveed A, Nadia H, Ishak A. Synthesis and characterization of thermo- and pH-responsive bacterial cellulose/ acrylic acid hydrogels for drug delivery. *Carbohydr Polym* 2012;88: 465–73.
- Naryan B, Jonathan G, Miqin Z. Chitosan-based hydrogels for controlled, localized drug delivery. *Adv Drug Deliv Rev* 2010;62: 83–99.
- Lee SC, Keun K, Kinam P. Hydrogels for delivery of bioactive agents: a historical perspective. *Adv Drug Deliv Rev* 2013;65: 17–20.
- Thomas B, Mieke V, Jorg S, et al. A review of trends and limitations in hydrogel-rapid prototyping for tissue engineering. *Biomaterial* 2012;33:6020–41.
- Cho E, Lee JS, Webb K. Formulation and characterization of poloxamine-based hydrogels as tissue sealants. *Acta Biomater* 2012; 8:2223–32.
- Sosnik A, Sefton MV. Semi-synthetic collagen/poloxamine matrices for tissue engineering. *Biomaterial* 2005;26:7425–35.
- Go DH, Joung YK, Lee SY, et al. Tertronic-oligolactide-heparin hydrogel as a multi-functional scaffold for tissue regeneration. *Macromol Biosci* 2008;8:1152–60.
- Suedee R, Bodhibukkana C, Tangthong N, et al. Development of a reservoir-type transdermal enantioselective-controlled delivery system for racemic propranolol using molecularly imprinted polymer composite membrane. *J Control Release* 2008;129:170–8.
- Maria DM-O, Carmen A-L, Angel C, Thorstein L. Cyclodextrin-based nanogels for pharmaceutical and biomedical applications. *Int J Pharm* 2012;428:152–63.
- Loira PC, Sapin MA, Diab R, et al. Low molecular weight heparin gels, based on nanoparticles for tropical delivery. *Int J Pharm* 2012; 426:256–62.
- Xi C, Li-Hua P, Ying-Hui S, et al. Astragaloside IV-loaded nanoparticle-enriched hydrogel induces wound healing and anti-scar activity through topical delivery. *Int J Pharm* 2013;447:171–81.
- Chang YG, QinJie W, YuJun W, et al. A biodegradable hydrogel system containing curcumin encapsulated in micelles for cutaneous wound healing. *Biomaterial* 2013;34:6377–87.
- Choi S, Baek E, Davaa E, et al. Topical treatment of the buccal mucosa and wounded skin in rats with a triamcinolone acetone-loaded hydrogel prepared using an electron beam. *Int J Pharm* 2013; 447:102–8.
- Hughes NE, Marangon AG, Wright AJ, et al. Potential food applications of edible oil organogels. *Trends Food Sci Tech* 2009;20: 47080.
- Schalink HM, van Malssen KF, Morgado-Alves S, et al. Crystal network for edible oil organogels: possibilities and limitations of the fatty acid and fatty alcohol systems. *Food Res Int* 2007;40:1185–93.
- Lupi FR, Garbriale D, Facciolo D, et al. Effect of organogelator and fat source on rheological properties of olive oil-based organogels. *Food Res Int* 2012;46:177–84.
- Terech P, Weiss RG. Low molecular mass gelators of organic liquids and properties of their gels. *Chem Rev* 1997;97:3133–59.
- Van EJH, Feringa BL. New functional materials based on self assembling organogels: from serendipity towards design. *Angew Chem* 2000;39:2263–6.
- Isabel FA, Bahia MF. Evaluation of the physical stability of two oleogels. *Int J Pharm* 2006;327:73–7.
- Sara DP, Sonia C, Agnese P, et al. Effect of monoglyceride organogel structure on cod liver oil stability. *Food Res Int* 2011;44: 2978–83.

35. Rocha JCB, Lopes JD, Mascarenhas MCN, et al. Thermal and rheological properties of organogels formed by sugarcane or candelilla wax in soybean oil. *Food Res Int* 2013;50:318–23.
36. Toro-Vazquez JF, Morales R, Alvarado ED, et al. Thermal and textural properties of organogels developed by candelilla wax in safflower oil. *J Am Oil Chem Soc* 2007;84:989–1000.
37. Esposito E, Menegatti E, Cortesi R. Design and characterization of fenretinide containing organogels. *Math Sci Eng C* 2013;33:383–9.
38. Kazunori I, Sumizawa T, Miyazaki M, Kakemi M. Characterization of organogel as a novel oral controlled release formulation for lipophilic compounds. *Int J Pharm* 2010;388:123–8.
39. Dassanayake LSK, Kodali DR, Ueno S. Formation of oleogels based on edible lipid materials. *Curr Opin Colloid Interface Sci* 2011;16:432–9.
40. Sinha VR, Maninder PK. Permeation enhancers for transdermal drug delivery. *Drug Dev Ind Pharm* 2000;26:1131–40.
41. Sushi IR, Santosh SB, Vaibhav U, et al. Lecithin organogel: a unique micellar system for the delivery of bioactive agents in the treatment of skin aging. *Acta Pharmaceut Sin B* 2012;2:8–15.
42. Rajiv K, Om PK. Lecithin organogel as a potential phospholipid-structured system for topical drug delivery: a review. *AAPS PharmaSciTech* 2005;6:298–310.
43. Shaikh IM, Jadhav KR, Gide PS, et al. Topical delivery of aceclofenac from lecithin organogels: preformulation study. *Curr Drug Deliv* 2006;3:417–27.
44. Willmann H, Walde P, Luisi L, et al. Lecithin organogels as matrix for transdermal transport drugs. *J Pharm Sci* 1992;81:871–4.
45. Masotti A, Vicennati P, Alisi A, et al. Novel Tween 20 derivatives enable the formation of efficient pH-sensitive drug delivery vehicles for human heptaoblastoma. *Bioorg Med Chem Lett* 2010;2:3021–5.
46. Marianecchi C, Carafa M, Marizo LD, et al. A new vesicle loaded hydrogel system suitable for topical applications: preparation and characterization. *J Pharm Pharmaceut Sci* 2011;14:336–46.
47. El-Laithy HM, Shoukry O, Mahran LG. Novel sugar esters proniosomes for transdermal delivery of vinpocetine: preclinical and clinical studies. *Eur J Pharm Biopharm* 2011;77:43–55.
48. Gannu PK, Pogaku R. Nonionic surfactant vesicular systems for effective drug delivery—an overview. *Acta Pharmaceut Sin B* 2011;1:208–19.
49. Agarwal R, Katara OP, Vyas SP. Preparation and in vitro evaluation of liposomal/niosomal delivery systems for antipsoriatic drug dithranol. *Int J Pharm* 2001;228:43–52.
50. Aranya M, Charinya C, Worapaka M, Jiradej M. Transdermal absorption enhancement of papin loaded in elastic niosomes incorporated in gel for scar treatment. *Eur J Pharm Sci* 2012;48:474–83.
51. Gonnet M, Lethuaut L, Boury F. New trends in encapsulation of liposoluble vitamins. *J Control Release* 2010;146:276–90.
52. Gupta PN, Mishra V, Rawat A, et al. Non-invasive vaccine delivery in transfersomes, niosomes and liposomes: a comparative study. *Int J Pharm* 2005;293:73–82.
53. Aranya M, Warintorn R, Masahiko A, et al. Transfollicular enhancement of gel containing cationic niosomes loaded with unsaturated fatty acids in rice (*Oryza sativa*) bran semi-purified fraction. *Eur J Pharm Biopharm* 2012;81:303–13.
54. Bangham AD, Standish MM, Walkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. *J Mol Biol* 1965;13:238–52.
55. Maria M, Chiara S, Donatella V, et al. Niosomes as carrier for tretinoin. I. Preparation and properties. *Int J Pharm* 2002;234:237–48.
56. Biswal S, Murthy P, Sahu J, et al. Vesicles of non ionic surfactants (niosomes) and drug delivery potential. *Int J Pharm Sci Nanotech* 2008;1:1–8.
57. Jia YF, Song YY, Pao CW, et al. In vitro skin permeation of estradiol from various proniosome formulations. *Int J Pharm* 2001;215:91–9.
58. Mahale NB, Thakkar PD, Mali RG, et al. Niosomes: Novel sustained release nonionic stable vesicular systems – an overview. *Adv Colloid Interface Sci* 2012;183–4:46–54.
59. Uchegbu IF, Florence AT. Non-ionic surfactant vesicles (niosomes): physical and pharmaceutical chemistry. *Adv Coll Interf Sci* 1995;58:1–55.
60. Kumar K, Rai AK. Proniosomal formulation of curcumin having anti-inflammatory and anti-arthritic activity in different experimental animal models. *Pharmazie* 2012;67:852–7.
61. Sankar V, Praveen C, Prasanth KG, et al. Formulation and evaluation of a proniosome hydrocortisone gel in comparison with commercial cream. *Pharmazie* 2009;64:731–4.
62. Ammar HO, Ghorab M, El-Nahas SA, Higazy IM. Proniosomes as a carrier system for transdermal delivery of tenoxicam. *Int J Pharm* 2011;405:142–52.
63. Ibrahim AA, Bosela AA, Ahmed SM, Mahrous GM. Proniosomes as a drug carrier for transdermal delivery of ketorolac. *Eur J Pharm Biopharm* 2005;59:485–90.
64. Frfkjaer S, Hjorth E, Writis O. Stability testing of liposomes during storage. In: Gregoriadis G, ed. *Liposome technology*. Florida: CRC Press; 1984:235–45.
65. Hatziantoniou S, Rallis M, Demetzos C, Papaioannou GT. Pharmaceutical activity of natural lipids on a skin barrier disruption model. *Pharmacol Res* 2000;42:55–9.
66. Zhang XL, Zhao R, Qian W. Preparation of an emulgel for treatment of aphthous ulcer on basis of carbomers. *Chin Pharm J* 1995;30:417–18.
67. Rahmani-Neishaboor E, Jallili R, Hartwell R, et al. Topical application of a film-forming emulgel dressing that controls the release of stratifin and acetylsalicylic acid and improves/prevents hypertrophic scarring. *Wound Repair Regen* 2013;21:55–65.
68. Mohamed MI. Optimization of chlorphenesin emulgel formulation. *AAPS J* 2004;6:81–7.
69. Khullar R, Kumar D, Seth N, Saini S. Formulation and evaluation of mefenamic acid emulgel for topical delivery. *Saudi Pharm J* 2012;20:63–7.
70. Stanos SP. Topical agents for the management of musculoskeletal pain. *J Pain Symptom Manage* 2007;33:342–55.
71. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. *Adv Drug Deliv Rev* 2012;64:175–93.
72. Lee EA, Balakrishnan P, Song CK, et al. Microemulsion-based hydrogel formulation of Itraconazole for topical delivery. *J Pharm Invest* 2010;40:305–11.
73. Dreher F, Walde P, Walther P, Wehrli E. Interaction of a lecithin microemulsion gel with human stratum corneum and its effect on transdermal transport. *J Control Release* 1997;45:131–40.
74. Perioli L, Pagano C, Mazzitelli S, et al. Rheological and functional characterization of new antiinflammatory delivery systems designed for buccal administration. *Int J Pharm* 2008;356:19–28.
75. Weiwei Z, Chenyu G, Aihua Y, et al. Microemulsion-based hydrogel formulation of penciclovir for topical delivery. *Int J Pharm* 2009;378:152–8.
76. Park US, Theraskin M, Antonio G, et al. Assessment of a new skin brightening emulgel containing glycolic acid, lactic acid, kojic acid, arbutin, and UVA/UVB filters in females with melasma. *J Am Acad Dermatol* 2012;66:AB178.
77. Feng G, Xiong Y, Wang H, Yang Y. Gelation of microemulsions and release behaviour of sodium salicylate from gelled microemulsion. *Eur J Pharm Biopharm* 2009;71:297–302.
78. Gannu R, Palem CR, Yamsani VV, et al. Enhanced bioavailability of lacidipine via microemulsion based transdermal gels: formulation optimization, ex vivo and in vivo characterization. *Int J Pharm* 2010;388:231–41.
79. Senhao L, Donggin Q. Preparation and in vitro evaluation of an ilomastat microemulsion gel by a self-microemulsifying system. *Pharmazie* 2012;67:156–60.
80. Barot BS, Parejiya PB, Patel HK, et al. Microemulsion-based gel of terbinafine for the treatment of onychomycosis: optimization of formulation using D-optimal design. *AAPS PharmaSciTech* 2012;13:184–92.
81. Boonme P, Suksawad N, Songkro S. Characterization and release kinetics of nicotinamide microemulsion-based gels. *J Cosmet Sci* 2012;63:397–406.
82. Chudasama A, Patel V, Nivsarkar M, et al. Investigation of microemulsion system for transdermal delivery of itraconazole. *J Adv Pharm Technol Res* 2011;2:30–8.
83. Luo M, Shen Q, Chen J. Transdermal delivery of paeonol using cubic gel and microemulsion gel. *Int J Nanomedicine* 2011;6:1603–10.
84. Araujo LMPC, Thomazine JA, Lopez RFV. Development of microemulsions to topically delivery 5-aminolevulinic acid in photodynamic therapy. *Eur J Pharm Biopharm* 2010;75:48–5.
85. Azeem A, Talegaonkar S, Negi LM, et al. Oil based nanocarrier system for transdermal delivery of ropinirole: a mechanistic,

- pharmacokinetic and biochemical investigation. *Int J Pharm* 2012; 422:436–44.
86. Kantaria S, Rees GD, Lawrence MJ. Gelatin-stabilised microemulsion based organogels: rheology and application in iontophoretic transdermal drug delivery. *J Control Release* 1999;60:355–65.
 87. Rhee GJ, Woo JS, Hwang SJ, et al. Topical oleo-hydrogel preparation of ketoprofen with enhanced skin permeability. *Drug Dev Ind Pharm* 1999;25:717–26.
 88. Almedia IF, Fernandes AR, Fernandes MR, et al. Moisturizing effect of oleogel/hydrogel mixtures. *Pharm Dev Technol* 2008;13: 487–94.
 89. Jibry N, Heenan RK, Murdan S. Amphiphilic gels for drug delivery, formulation and characterization. *Pharm Res* 2004;21:1851–61.
 90. Uros M, Aliaz G, Marian B, Odon P. Novel hybrid silica xerogels for stabilization and controlled release of drug. *Int J Pharm* 2007;330: 164–74.
 91. Guenther U, Smirnova I, Neubert RHH. Hydrophilic Silica aerogels as dermal drug delivery systems- Dithranol as a model drug. *Eur J Pharm Biopharm* 2008;69:935–42.
 92. Alnaief M, Antonyuk S, Hentzschel CM, et al. A novel process of coating of silica aerogel microspheres for controlled drug release applications. *Microporous Mesoporous Mater* 2012;160: 167–73.
 93. Garcia-Gonzalez CA, Uy JJ, Alnaief M, Smirnova I. Preparation of tailor made starch based aerogel microspheres by the emulsion-gelation method. *Carbohydr Polym* 2012;88:1378–86.
 94. Smirnova I, Tuerk M, Wischumerski R, Wahl AM. Comparison of different methods for enhancing the dissolution rate of poorly soluble drugs: case of griseofulvin. *Eng Life Sci* 2005;5:277–80.
 95. Alnaief M, Alzaitoun M, Garcia Gonzalez CA, Smirnova I. Preparation of biodegradable nanoporous microspherical aerogel based on alginate. *Carbohydr Polym* 2011;84:1011–18.
 96. Cheng Y, Lingbin L, Wuyuan Z, et al. Reinforce low density alginate based aerogels: preparation, hydrophobic modification and characterization. *Carbohydr Polym* 2012;88:1093–9.
 97. Ollio A, Ollio J. The preparation of lignocellulosic aerogels from ionic liquid solutions. *Carbohydr Polym* 2009;75:125–9.
 98. Garcia GCA, Alnaief M, Smirnova I. Polysaccharide based aerogels-promising biodegradable carriers for drug delivery systems. *Carbohydr Polym* 2011;86:1425–38.
 99. Cardea S, Pisanti P, Reverchon E. Generation of chitosan nanoporous structure for tissue engineering applications using a supercritical fluid assisted process. *J Supercrit Fluids* 2010;54:290–5.
 100. Anja V, Zeljko K, Zoran N. Preparation of multi-membrane alginate aerogels used for drug delivery. *J Supercrit Fluids* 2013;79: 209–15.