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Review
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Review

Vesicular drug delivery for the treatment of topical disorders: current and future perspectives

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Abstract

Objectives Vesicular drug delivery has become a useful approach for therapeutic administration of pharmaceutical compounds. Lipid vesicles have found application in membrane biology, immunology, genetic engineering and theragnostics. This review summarizes topical delivery, specifically dermal/transdermal, ocular and transungual, via these vesicles, including future formulation perspectives.

Key findings Liposomes and their subsequent derivatives, viz. niosomes, transferosomes, pharmacososmes and ethosomes, form a significant part of vesicular systems that have been successfully utilized in treating an array of topical disorders. These vesicles are thought to be a safe and effective mode of improving the delivery of lipophilic and hydrophilic drugs.

Summary Several drug molecules are available for topical disorders. However, physicochemical properties and undesirable toxicity have limited their efficacy. Vesicular delivery systems have the potential to overcome these shortcomings due to properties such as high biocompatibility, simplicity of surface modification and suitability as controlled delivery vehicles. However, incorporating these systems into environmentally responsive dispersants such as hydrogels, ionic liquids and deep eutectic solvents may further enhance therapeutic prowess of these delivery systems. Consequently, improved vesicular drug delivery can be achieved by considering combining some of these formulation approaches.

Keywords: vesicular drug delivery; topical disorders; dermal; ocular; transungual; liposomes

Introduction

Transdermal drug delivery has become an alternative to the traditional oral drug delivery route of administration, in addition to offering an alternative to hypodermic injections.[1] Specifically, transdermal drug delivery has numerous benefits in comparison to oral drug delivery, including bypassing first-pass metabolism, which leads to sudden drug metabolism and thus reduced bioavailability.[2] In addition, transdermal delivery avoids the shortcomings of hypodermic injections, such as pain at the injection, high discomfort and the severe threat posed by medical waste and disease transmission following re-use of needles. Furthermore, transdermal drug delivery systems can be self-administered and are inexpensive. However, the number of drugs that can be adapted for transdermal delivery present as a limitation for this route of administration. Over the past decades, technological advancements and innovations within existing drug delivery techniques have led to the successful development of drugs with adequate molecular dimensions or delivery systems for efficient transdermal drug delivery. In general, transdermal drug delivery is categorized into three generations (Table 1).[3]

In recent years, vesicular delivery has become a useful approach to drug delivery. Lipid vesicles have gained interest in immunology, membrane biology, theragnostic and genetic engineering research. Vesicles have also been used in biological layer modelling and targeted transport for API.[4–7]

Biological membranes are universal defining structures that surround and compartmentalize all cells and organelles.[1] The lipidic bilayer organization is the only feature common to all biological membranes. Experimental models explaining the motional dynamics and stationary structures of some isolated partitions of biological membranes and lipid vesicles are among the various types of experimental models for understanding bio-membranes. Despite being developed for rudimentary research, numerous technological advancements have surfaced due to using these models.[1] Subsequently, they have led to lipid vesicles successfully evolving as suitable vehicles for controlled delivery.[1] The advantages and disadvantages of some lipid-based vesicular drug delivery system are extensively summarized in Table 2. In addition, formulation strategies to enhance therapeutic prowess of vesicular delivery systems, including incorporating them into environmentally responsive dispersants such as hydrogels, ionic liquids and deep eutectic solvents, are discussed herein.

Significant manuscripts cited in this review and findings from these publications are highlighted in Table 3. A PRISMA flow diagram (Figure 1) was used to facilitate the extraction of manuscripts from electronic databases. The titles and abstracts of the extracted articles were screened for relevance, which led to the elimination of duplicates.

Table 1 Types of transdermal drug delivery systems[2, 3]

Transdermal drug delivery system (TDDS)	Description	Advantages	Limitations
First generation	Comprises of transdermal patches for clinical use. The drug should be of low-molecular weight, efficacious at low doses and lipophilic.	• High bioavailability as opposed to oral bioavailability. • No pricking required.	• Not feasible for drugs with high molecular weight. • Stratum corneum limits drug permeability. • Not suitable for hydrophilic drugs.
Second generation	Chemical enhancers are generally utilized effectively to improve skin permeability through reversal disruption of the stratum corneum to promote deeper skin penetration of the drug. Iontophoresis is another second-generation TDDS that does not alter the skin barrier but helps in the movement of charged drug through electrophoresis. Non-cavitational ultrasound is another skin permeation enhancing method, which is an effective second-generation TDDS. This is an oscillating wave of pressure at a frequency that is intensely high for the human ear. This oscillation and the creation of a pressure gradient drive drug penetration into the skin while disrupting the stratum corneum.	• Easy penetration of high molecular weight drugs through the stratum corneum following disruption of an ordered bilayer structure of the intracellular lipids found within the skin layer. • Iontophoresis offers high control over drug dosing by scaling the adequate amount of charge delivered to the skin. • Provides rapid onset of drug response. • Non-cavitational ultrasound allows for deeper skin penetration of the drug	• Increased risk of skin irritation from chemical enhancers. • Iontophoresis is costly. • Non-cavitational ultrasound is limited to lipophilic and small drug molecules. • Non-cavitational ultrasound can also cause damage to deeper skin tissues.
Third generation	Third generation systems induce significant impacts on the stratum corneum via stronger disruption while protecting deeper skin tissues. Third generation delivery systems include amalgamation of different chemical enhancers, biochemical enhancers, electroporation, cavitational ultrasound, microneedles, thermal ablation and microdermabrasion.	• Suitable for narrow and specific combination of drugs. • Proved the highest skin permeability without damaging or causing skin irritation.	• Expensive • Require technical expertise. • Limited clinical use.

Table 2 Advantages and disadvantages of vesicular drug delivery system[8–10]

Drug delivery systems (DDS)	Description	Advantages	Disadvantages
	Vesicular delivery systems are highly ordered assemblies comprising one or multiple concentric bilayers formulated as an outcome of self-assembling of amphiphilic building blocks in water. These systems are critically essential for targeted drug delivery because they possess specific capability to localize drug activity at the organ or site of action, hence reducing the concentration at other body sites. Vesicular DDS hold the potential to sustain drug levels at a predetermined rate (zero-order kinetics) and maintain efficient drug concentration within the body thus limiting side effects.	• Encapsulation of both hydrophilic and hydrophobic drugs. • Improves the bioavailability of the drugs. • Delays the elimination of rapidly metabolizable drugs. • Prolongs the circulation of drugs within the body. • Helps in the accomplishment of targeted drug delivery. • Assists in resolving drug stability issues. • Facilitates the elimination of toxicity concerns for certain drugs.	• Some vesicular DDS (niosomes, transferosomes, liposomes) are externally triggered and require pH, temperature, or even magnetic sensitivity for passive transportation of drugs, limiting the overall loading capacity of the drug during preparation, *in vivo* transportation and preservation.
Liposomes	Liposomes are considered concentric, colloidal bilayer vesicles whose aqueous compartment is completely enclosed within a bilayer membrane, mainly comprising of synthetic or natural lipids.	• Suitable for delivering lipophilic and hydrophilic drugs. • Enhance stability while protecting the encapsulated drugs from the external environment. • Reduces drug toxicity. • Limits the exposure of sensitive tissues to toxic drugs as well as their metabolites. • Suitable for the delivery of small molecular weight drugs in addition to high molecular weight drugs. • Assist in the accomplishment of targeted specific drug delivery. • Increases pharmacokinetic features of drugs by limiting their elimination and improving systemic circulation.	• Liposomes are leaky thus causing premature release of drug. • Poor encapsulation efficiency for hydrophilic molecules. • Expensive. • Short shelf life. • High production cost.
Ethosomes	Ethosomes are lipid carriers with high permeability and drug-delivery capability due to high ethanol concentration.	• Suitable for delivering lipophilic and hydrophilic drugs. • Optimal encapsulation efficiency as opposed to liposomes. • Cost-effective and simple method of preparation. • High deformability and elasticity with deeper skin penetration in comparison to liposomes	• High skin irritation due to high ethanol concentration.
Niosomes	Niosomes are relatively modern vesicular DDS which comprise unilamellar or sometimes multimellar vesicles. Niosomes are non-ionic surfactant vesicles, which consist of microscopic lamellar vesicles formulated when a non-ionic surfactant (primarily alkyl/dialkyl polyglycerol ether) is added into cholesterol with substantial hydration within the aqueous media. Cholesterol addition offers high rigidity to the bilayer membrane giving rise to less permeable niosomes while non- ionic surfactants enhance the vesicle size and offer charge therefore improving entrapment efficiency.	• More stable in comparison to liposomes. • Niosomes do not require any specialized handling and storage conditions. • Osmotically active. • These particles can entrap drugs with a broad solubility range. • Niosomes serve as a depot system for sustained drug release when there is a need. • The design is more flexible in terms of structure in comparison to liposomes. • Niosomes lead to improved topical, oral, as well as parenteral drug bioavailability. • Therapeutic efficiency of the entrapped drug is improved through limiting impact with target cells while minimizing drug clearance.	• Hydrolysis of encapsulated drug which reduces the shelf-life of the dispersion.

Table 2 Continued

Drug delivery systems (DDS)	Description	Advantages	Disadvantages
Transferosomes	Noisomes and liposomes have limited skin permeability and are generally not feasible for transdermal drug delivery. Transferosomes are regarded as stress responsive, ultra-deformable, complicated vesicles having an aqueous core which is surrounded by a complex lipid bilayer. Artificially made vesicles comprise of a natural amphiphilic lipid which is complemented by a bilayer softener which is a bio-compatible surfactant which allows transferosomes to alter their membrane composition in a reversible manner, allowing narrow skin pore penetration.	• Transferosomes are deformable, thus can penetrate minute and narrow pores found in the skin irrespective of measurable loss. • Efficient entrapment of both small and high molecular weight drugs. • Protection of encapsulated drug from metabolic enzymatic degradation. • Effectively utilized in systematic and topical drug delivery. • Can act as a drug depot delivery system.	• Chemically unstable. • Expensive and costly. • Phospholipid purity is questionable.
Aquasomes	Aquasomes are termed as "water bodies" which are triple layered self-assembled nanostructures constituting of a solid nanocrystalline core that has an oligomeric film coating which helps in the absorption of biochemically active drug molecules irrespective of any modification.	• Assist in the preservation of the conformational integrity and biochemical stability of bioactive molecules. • Due to their composite structure, size and stability, these molecules avoid environmental degradation and reticuloendothelial clearance. • Possess similar physical properties as colloids. • As suspensions of aquasomes constitute of bio-degradable nanoparticles of colloidal range, they are highly concentrated in the muscles and the liver. • Drugs are absorbed topically instead of after internal breakdown or alternation as seen in antigen or insulin delivery, hence biological or pharmacological activity is immediately accomplished.	• Transfer efficiency is low. • Expensive and costly so not economically viable.
Colloidosomes	These are advanced vesicular DDS designed for the delivery of vitamins, proteins and other food supplements. Colloidosomes comprises of hollow shell microcapsules which consists of fused or coagulated particles at the interface of emulsion droplets.	• High flexibility due to their small size which facilitates better applications and is considered as the choice of DDS for the encapsulated material. • Controlled drug permeability. Permit selective and time bound release of encapsulated material. • Easy to formulate. • High mechanical strength, good at yielding stress while withstanding the mechanical load. • Sensitive and fragile material such as cells and biomolecules are easily encapsulated.	• Produce poor yield. • During transference of the colloidosomes to aquatic media from the organic media, a significant proportion is lost.
Cubosomes	Cubosomes self-assemble, in the presence of a polar solvent, into a line of thermodynamically stable liquid crystalline phases. Such crystalline phases with equivalent lengths contain adequate extent of molecular orientation in addition to structural symmetry.	• Ability for targeted release in addition to controlled drug release. • Amphiphillic, hydrophobic and hydrophilic drugs are very easily encapsulated • Easy preparation of the skin. • Biodegradable. • High bio-adhesive nature is exhibited by the cubic phases, so they are considered as more convenient for the mucosal and topical drug delivery system.	• Expensive and costly. • Limited yield.

Table 2 Continued

Drug delivery systems (DDS)	Description	Advantages	Disadvantages
Sphingosomes	These are concentric, colloidal, bilayered vesicles whose aqueous compartment is completely enclosed within the bilayer membrane which primarily constitutes of synthetic or natural sphingolipids.	• Better retention of the drug than other vesicular DDS • These can be efficiently utilized for intravenous, subcutaneous, intramuscular, oral and transdermal routes of drug administration. • Offer selective passive drug targeting to tumour cells. • Therapeutic index and efficacy of the encapsulated drug is improved. • Increased stability through encapsulation. • Reduced drug toxicity following encapsulation. • Enhanced pharmacokinetics of encapsulated drug thus enhanced circulation time. • Design flexibility promotes site specific ligand binding to accomplish active targeting.	• Highly expensive so not economically feasible. • Limited entrapment efficiency.
Ufosomes	Ufosomes were created to improve drug penetration into the skin via the stratum corneum. Ufosomes are equipped with a lipid carrier which gets attached to the surface of the skin and promotes the exchange of lipids between the outermost stratum corneum	• Better stability than liposomes. • Better entrapment efficiency for hydrophobic and hydrophilic drugs. • Cheaper than liposomes.	• Poor deeper penetration. • Variable drug levels • Limited bioavailability.

Topical Drug Delivery Systems

Challenges and opportunities for topical drug delivery

Dermal/transdermal drug delivery systems

The main challenge for topical applications is the dermal penetration of the hard horny layer/stratum corneum (SC), which is the top-most layer of the skin.[11] These skin structures act as a rate-limiting step for epidermal drug transfer.[12] Additional considerations in topical delivery of drug molecules include physicochemical aspects of the drug, such as log P, pKa, solubility and molecular mass.[12–14] For an API to be effective when applied topically, the API molecules must have a size <500 Da to enable diffusion across the SC, thereby penetrating to the site of action.[2, 15] This molecular size consideration is also an aspect that can be challenging when developing topical formulations. Moreover, formulations must have aqueous and lipid solubility action.[12, 15] Patient individual variability regarding skin in both healthy and diseased skin may also influence the efficacy of API.[16] These unique variations are caused by biological factors and include skin hydration, gender, age, ethnicity and metabolism.[16, 17] For example, some enzymes in the skin may metabolize some drugs before cutaneous absorption can occur. Local skin irritation, such as irritant and allergic contact dermatitis, at the site of delivery can also pose a substantial challenge for topical applications.[18] Other disadvantages of topical formulations include being time-consuming to apply; the regimen can also be complicated, messy and uncomfortable.

Two mechanisms of vesicle absorption have been proposed for transdermal vesicular drug delivery, viz. the diffusion of intact vesicles through the SC and the formation of new vesicles from individual components of the formulation.[19] The latter phenomenon occurs only in certain regions within the SC, specifically where water content is high. This phenomenon is highly postulated since the vesicles' diameter is greater than the lamellar spaces of the lipid within the SC.[19]

In humans, liposomes have shown to be superior in delivering methotrexate and refining its activity for transport resistant leukemic cell lines compared to non-entrapped methotrexate formulations.[20] A dual deformable liposomal ointment has also been used to successfully penetrate retinoic acid and epidermal growth factor to enhance healing in burn wounds.[21] In the cosmetic industry, liposomal and niosomal formulations containing urea were manufactured for use.[22] The optimized niosomal formulation was the best moisturizing dermato-cosmetic, while the optimized liposomal formulation also outperformed the conventional formulation.[22] In an attempt to treat pattern baldness, minoxidil was incorporated into niosomes. The study revealed that the niosomal formulations of minoxidil improved follicular delivery by substantially increasing the partition of minoxidil in the aqueous canal of the human hair.[23] In dolor treatment, the selective cyclooxygenase-2 (COX-2) inhibitor, nimesulide, was successfully encapsulated into niosomes for transdermal delivery and exhibited enhanced anti-inflammatory properties when compared to delivery of nimesulide from conventional technologies.[24]

Similarly, the non-steroidal inflammatory drug ketorolac was successfully entrapped in niosomes, significantly improving permeation and reducing the lag time post-application.[25] Niosomes formulated using α-omega-hexadecyl-bis-(1-aza-18-crown-6) or Bola, Span 80 and cholesterol in a 2 : 5 : 2 molar ratio were proposed as a suitable delivery system for 5-fluorouracil (5-FU) for use in therapy for various skin cancers. This formulation exhibited increased cytotoxic effects by up to 8-fold and an increased solubility and permeability

Table 3 Summary of significant review manuscripts

Author(s)/year	Aim	Research method	Key findings
Vitorino *et al.* (2015)[11]	To investigate different methods of permeation enhancement by combining lipid nanoparticles with conventional chemical enhancers.	Secondary qualitative review	The majority of approaches commonly utilized in transdermal delivery of drugs have advantages and disadvantages; therefore, further research is required for efficient drug delivery. The skin barrier is considered a formidable obstacle for drug delivery; however, new multicomponent technologies have combined several strategies, which have been reported to provide promising results for drug delivery.
Haque and Talukder (2018)[13]	To review available knowledge related to the skin-chemical enhancer interaction for designing a topical and transdermal formulation.	Secondary qualitative review	Out of all approaches which can be utilized for enhancing penetration of drug molecules across the skin, chemical enhancers have been reported to have more efficiency due to their capability to improve molecule permeation.
Bolzinger *et al.* (2012)[12]	To analyse the mechanism of penetration of drugs through the skin.	Secondary qualitative review	Due to the heterogeneous structure of the skin, there are a number of penetration routes. The analysis of penetration mechanisms reveals that controlling the intercellular penetration route using crystalline lipids, and penetration via skin appendages, are likely contributors of efficient drug penetration.
Benson *et al.* (2019)[14]	To discuss the evolution of the principles of percutaneous absorption and skin products from recent times to date.	Secondary qualitative review	Skin application products range from simple solutions and ointments to nanotechnologies. However, the products applied to the skin for cosmetic or for treatment purpose must fulfil safety requirements.
Singh and Morris (2011)[16]	Analysis of biological factors that contribute to variations in transdermal permeation of drugs across human skin. Analysis of currently available transdermal therapeutic systems which might be efficient in reducing biological factors which cause variations.	Secondary qualitative review	There is a significant requirement to take preventive steps to avoid harmful generalizations when prescribing transdermal products. The patient information leaflet must always include specific instructions, including the application and duration of application.
Paudel *et al.* (2010)[18]	To provide an overview of transdermal products presented within the market and in clinical trials, and to focus on the challenges and solutions for overcoming the problems of skin irritation and skin permeation.	Secondary qualitative review	The emergence of skin permeation enhancement techniques and reducing skin irritation would improve the transdermal market for macromolecules, hydrophilic compounds and conventional drugs.
Paolino *et al.* (2008)[26]	To improve the cytotoxic drug effect towards various types of skin cancer cell lines by utilizing bola-niosomes.	Experimental research	The research outcomes revealed that technological features of bola-niosomes are encouraging and can be applied to treat a number of cancerous skin diseases.
Mohanty *et al.* (2018)[28]	To focus on different aspects of ethosomes, such as their penetration mechanism, preparation, composition, advantages, application characterization and the availability of marketed products.	Secondary qualitative review	Due to having malleable vesicles, ethosomal carriers provide new opportunities for developing novel improved therapies. However, at the same time, it is significant to deal with the challenges associated to ethosome-based therapies.
Wang *et al.* (2020)[31]	To enhance the therapeutic efficiency of psoriasis based on trans-retinoic acid and betamethasone by formulating a dual-loaded flexible liposomal gel.	Experimental research	The outcomes of the research revealed that the flexible dual-loaded liposomal gel provided a synergistic effect. This effect was found as an efficient topical therapy for psoriasis treatment.
Amnuaikit *et al.* (2018)[34]	To develop as well as to characterize phenylethyl resorcinol-loaded transferosome and invasome drug delivery systems.	Experimental research	The elastic vesicle carriers, viz. invasomes and transferosomes were an appropriate delivery system for phenylethyl resorcinol, which has been widely utilized as a skin lightening agent.

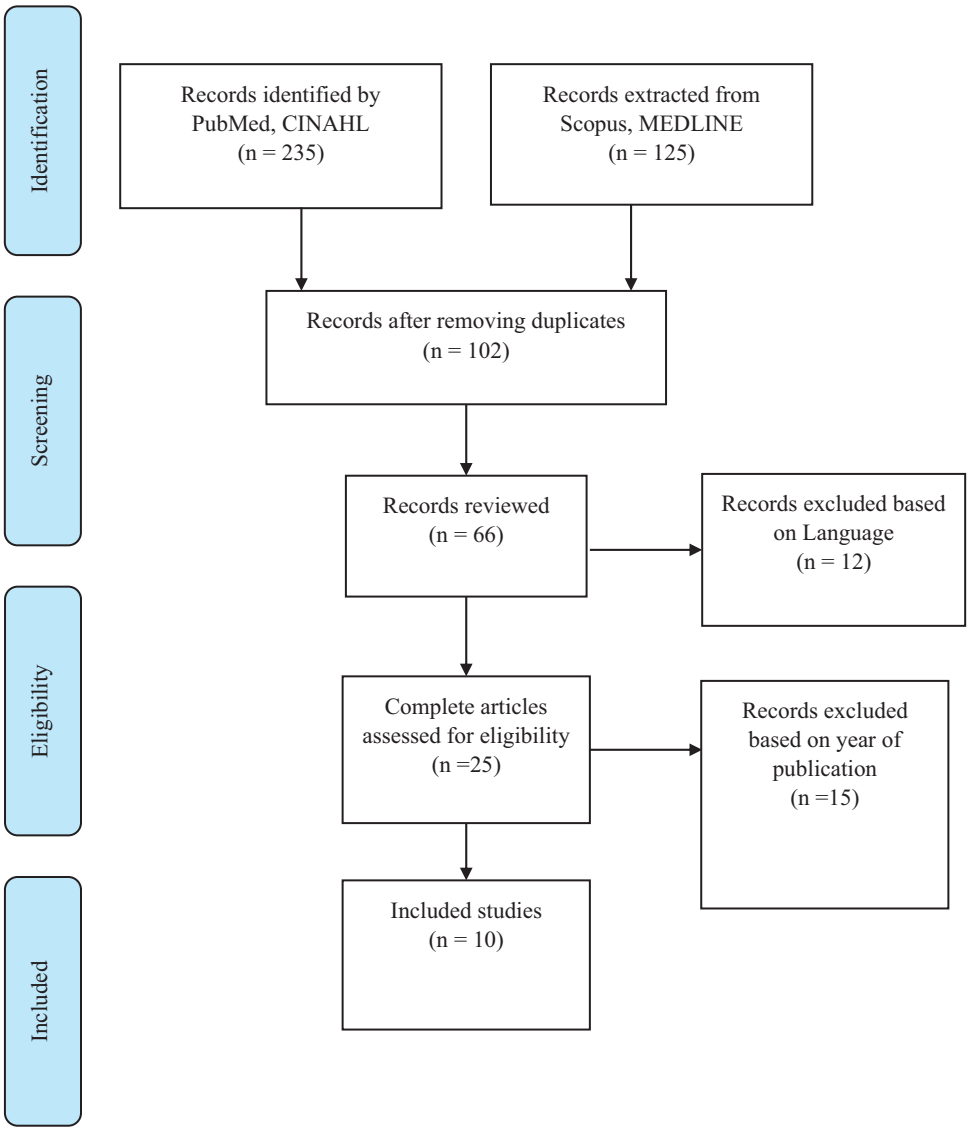

Figure 1 PRISMA flow diagram for significant review manuscripts.

of up 4-fold compared to conventional technologies.[26] Novel elastic niosomes using Tween 61 and ethanol were developed to enhance the transdermal delivery of diclofenac diethylammonium and the anti-inflammatory effect of the molecule.[27]

Ethanol-containing elastic vesicles interact with the lipid molecules in the skin resulting in an increased fluidity of the SC and a decrease in the density of the multiple lipid layers of cell membranes, thereby enhancing the inter- and intra-cellular permeability of the vesicles. The use of ethanol also improves the vesicular membrane's elasticity and facilitates entry of vesicles into the SC and deeper/inward layers of the skin.[28, 29] An optimized ethosomal formulation for the delivery of lamivudine showed 25 times greater transdermal flux across rat skin than that of a lamivudine solution. Microscopic studies revealed that ethosomes reached the intercellular regions of the skin's deeper layers and ethosomes exhibited significantly higher intracellular uptake viz. 85.7% when compared to API solution viz. 24.9%.[30] Flexible liposomes containing alcohol showed the best transdermal efficiency for encapsulated retinoic acid for psoriasis treatment through close contact with the surface of the skin and reduction of trans-epidermal water loss.[31]

Novel transferosomes were found to penetrate the skin's deep layers[28, 32] and reach the systemic circulation following topical application. Transferosomes can spontaneously and easily penetrate the intact SC via the intracellular or trans-cellular routes of penetration due to their elastic nature. The latter is achieved by modification of the intercellular lipid lamellae, which in turn facilitates the penetration of free API molecules.[33]

In a B16 melanoma cell model, transferosomes and invasomes exhibited more significant tyrosinase inhibition activity and melanin reduction than the liposomes.[34] The increased solubility, stability and skin permeation were corroborated in a study undertaken using calcein and carboxyfluorescein as the encapsulated API.[35]

Ocular

Ocular/opthalmic delivery is among the most promising yet challenging modes of drug delivery.[36] This challenge poses an excellent opportunity for the rational design of novel and significantly improved ocular delivery systems. The main challenge of designing an effective drug delivery system is to achieve an optimally safe drug concentration at the active site for the required duration to provide

high therapeutic efficacy. The natural distribution of aqueous humor and tear fluid decreases the contact time of topically delivered API. In addition, other ocular barriers in the corneal and conjunctival epithelia and the retinal pigment epithelium hinder the transportation of drug molecules.[36, 37] These factors lead to low bioavailability of drugs from ocular therapy, and only a minute quantity of the drug is absorbed. It is estimated that only about 1–5% of the drug instilled into the eye is absorbed.[37, 38]

For certain drug molecules, regular instillation of eye drops is necessary to achieve and thus maintain a therapeutic concentration of API at the site of action or in the tear film. The periodic instillations are necessitated by the rapid elimination of the drug through blinking and tear flow, resulting in reduced therapeutic efficacy.[37] The frequent use of highly concentrated solutions to achieve the desired therapeutic results may cause toxic effects and impairment of cells at the ocular surface. Consequently, the time of residence of the API in the tear film must be maximized to exert an efficacious and therapeutic local effect. Moreover, reduced dosing of ocular preparations may enhance patient adherence. Therefore, ocular delivery systems such as polymeric inserts, aqueous gels, emulsions, suspensions, ointments and viscous solutions have been developed to maximize the bioavailability of API delivered via the aforementioned route.[39, 40]

Micro- and nano-particulate delivery systems are utilized to improve the residence time of drug molecules on ocular surfaces via the interaction of functional groups and surface charges of these systems with the mucin layer, ultimately prolonging the interaction of the formulation at the corneal surface.[41, 42] Entrapment of API into nanoparticles to shield them from degradation by enzymes has successfully been achieved. Consequently, this approach permits reduced doses to attain therapeutic efficacy and prevents undesirable side effects.[42, 43]

Dai *et al.*[44] investigated liposomes for ophthalmic delivery. The authors used liposomes containing bile salts to deliver tacrolimus in an attempt to improve corneal permeability. Liposomes synthesized with sodium taurocholate and sodium glycocholate were postulated as viable API carriers in ocular delivery. This was attributed to low toxicity and improved permeability. Non-toxic liposomal formulations containing minocycline designed for ocular use were found to deliver 40% of the API to the retina post-sub-conjunctival injection.[45]

The delivery of timolol maleate in niosomes appeared to be better than using conventional delivery approaches for timolol.[46] Studies involving the delivery of gentamycin and pilocarpine as niosomal formulations revealed a better pharmacodynamic response than when conventional delivery technologies were used.[47–49] Multilamellar niosomes showed to be a promising carrier for ocular delivery of acetazolamide. In vivo characterization of these niosomes revealed a considerable reduction in intraocular pressure compared to a simple solution of acetazolamide.[50]

Novel Spanlastics were manufactured to overcome the challenges associated with fluconazole and decrease the toxicity levels observed when a fluconazole solution was administered. The VDDS did not exhibit any cytotoxic effects and showed a tripled increase in ocular permeability compared to the commercially available Zocon (fluconazole, 0.3% w/v) formulation.[51]

Transungual drug delivery systems

Diseases that affect the human nail range from mild pigmentation due to smoking to more severe infections and inflammation. Onychomycosis and nail psoriasis are the most common.[52, 53] Historically, nail disorders have been treated using a combination of systemic antifungals or local antimycotics, steroids or vitamins.[54] Systemic therapies to treat nail disorders are associated with incidences of systemic side effects and drug interactions. This challenge can be resolved by topical transungual drug delivery systems.[55]

The nails' horny structure is the main challenge with regards to topical drug delivery. The compact, highly keratinized nail plate hinders drug permeability and uptake into the nail(s). The stable disulfide bonds in the nail plate are responsible for causing the nail's hardness and, in turn, restricts the penetration of the drugs.[56] The low permeability and poor drug uptake can be attributed to the nail plate structure, composed of compact keratin molecules with disulfide bonds. Together, they are responsible for the hardness of the nail and provide a significant barrier to drug permeation.[56, 57]

Transungual delivery provides localized drug delivery, promotes patient compliance due to the technology's non-invasive nature and reduces systemic effects, potentially making it a cost-effective drug delivery approach.[52, 54] Despite the benefits of transungual drug delivery in treating nail disorders, the low permeability of topical drugs across the nail plate warrants further research and development into this technology.[54]

As alluded to above, transungunal drug delivery and drug efficacy are related to the physicochemical properties of the drug molecule and the formulation characteristics.[58, 59] Targeting any of these parameters through physical or chemical techniques may improve the permeability, and consequently, the effectiveness of the drug.[53]

The physical techniques include reducing the nail thickness by filing, direct penetration of the nail plate and delivery of the drug via microporation, and disruption of the keratinized structure of the nail plate using laser energy or low-frequency ultrasound.[55, 60]

The chemical techniques used to improve transungual permeability include using nail softeners such as urea, salicylic acid in combination with N-(2-mercaptopropionyl) glycine and water. These agents result in swelling and the formation of the pores in the nail plate, thus increasing the permeability of the drug. Drug permeability may also be improved by breaking down the keratin-disulfide matrix of the nail plate using keratolytic enzymes and chemicals that cleave disulfide bonds such as N-(2-mercaptopropionyl) glycine, N acetylcysteine, sodium sulfite and hydrogen peroxide.[52, 60] Permeation enhancers, polyethylene glycols and inorganic salts such as sodium phosphate have been found to increase transungual drug permeation by moisturizing the nail plate, altering the keratin matrix and increasing thermodynamic activity of the API following interaction with an inorganic salt.[52, 60] The success of transungual therapy may also be increased by using large amounts of a drug molecule to maintain sufficient therapeutic drug concentrations and compensate for the loss of drug due to everyday activity, the extent of drug–keratin binding and clearance of the drug.[61]

Nanoparticles (NP) are among novel strategies to overcome challenges in transungual drug delivery.[52] As nanoparticles are smaller in size than other drug formulations, drugs formulated as nanoparticles easily diffuse through the keratin network as the permeability coefficient is increased with a decrease in the molecular size of diffusing molecules.[62] NP have found use in delivering targeted antifungal therapy, permitting the release of concentrated API while maintaining a low administration dose. The increased dose at the site of action can wipe out the infecting fungi before developing resistance, thereby overcoming this vexing issue and improving the side effect profile.[63]

Liposomal and ethosomal formulations for transungual delivery have been attempted in the treatment of nail disorders using caffeine

as the model API.[64] The outcomes of the study suggested that liposomes and ethosomes could enhance penetration of hydrophilic substances through the nail plate, and both systems can be used for topical treatment of nail disorders.[64]

To date, topical therapy for onychomycosis with terbinafine hydrochloride (TBF-HCl) is non-existent. A novel liposome film preparation containing TBF-HCI was made for simple and painless application for an extended period on the nail plate to improve drug penetration through the nail plate. In addition, the adhesive properties of the technology were found to be adequate as a simpler topical treatment.[65] The aforementioned study developed a novel experimental animal model using *Trichophyton mentagrophytes* without using an immunosuppressed agent. In vivo investigations concluded that the TBF-HCl loaded liposome film preparation can be recommended as an auspicious system for ungual treatment of onychomycosis.[65]

Similarly, Ghannoum *et al.*[66] attempted to incorporate TBF into transferosomes to enhance the ability to treat onychomycosis. The results suggested that the potent inhibitory and fungicidal activity of TBF, combined with the ability of transferosomes to provide targeted drug delivery to the nail bed, could provide a potential clinically beneficial alternative for the treatment of onychomycosis.

Shah *et al.*[67] conducted a study to encapsulate TBF-HCl into liposomes and subsequently load the liposomes into a nail lacquer. The results concluded that the permeation of TBF-HCl through the human nail plate was improved significantly when applied as a liposome-loaded preparation compared to TBF-HCl lacquer containing a penetration enhancer.[67] Therefore, liposome-in-lacquer preparations can provide a more refined approach for transungual delivery which can ultimately be considered for administering API utilized explicitly in nail disorders.[67]

Novel Approaches to Vesicular Drug Delivery

Environmentally responsive dispersants

Recently, there has been enormous progress in drug delivery subsequent to the discovery of liposomes and other VDDS. However, there is still a continued necessity for enhancements to fight the drawbacks exhibited by these delivery systems. The stability issue of liposomes and related vesicles remains an aspect that is encircled by various problems. Among which, the formation of ice crystals in liposomes,[68] physical and chemical instability of VDDS due to oxidation of cholesterol and phospholipids,[68] and seepage of entrapped API.[69, 70] Pharmacosomes do not exhibit loss of drug leakage due to the covalent bod between the API and the phospholipids used in manufacture.[1, 8]

Several attempts have been proposed and undertaken to improve the stability of vesicles and enhance drug efficiency in lipid vesicles. The use of environmentally responsive dispersants (ERD) such as hydrogels have been shown to provide the best solution to tackle such challenges.[71, 72]

Thermo-responsive hydrogels

Thermosensitive hydrogel systems provide an opportunity to deliver a liquid solution or suspension containing a payload that, once administered, forms an in-situ gel at the site of administration when a specific target temperature is reached. These systems are injectable fluids that can be presented into the body in a minimally invasive way before gelling within the desired organ, tissue or body orifice. These gelling systems present numerous benefits compared to delivery technologies preshaped in their final form before insertion. For instance, injectable fluids do not require surgical interventions for implantation or removal if non-biodegradable materials are used. In addition, different therapeutic agents can be integrated using simple processes such as blending. When used to fill cavities or a flaw, their flowable nature ensures a perfect fit.[73]

Poly (N-isopropyl acrylamide) (pNIPAAM) is a polymer with thermosensitive properties. It displays a critical solution temperature at 32°C which may be offset to physiological values. This can be achieved by including surface active agents or polymers in the formulation. These polymers display distinctive qualities with respect to the sharpness of an almost discontinuous transition and render pNIPAAM a suitable carrier to contemplate in situ gelling drug delivery. The gelation of 5% w/v polymer solutions occurs at different temperatures in phosphate-buffered saline (PBS). At 27°C, the transparent solution becomes cloudy and eventually solidifies to form a gel on further heating.[74]

Triblock copolymers of polyethylene glycol-b-polypropylene glycol-b-polyethylene glycol (-PEO-PPO-PEO-), commercially available as grades of Pluronic or Poloxamer, are non-ionic, water-soluble materials that have been used as pharmaceutical excipients. The polymers are amphiphilic, display properties related to surfactants and are able to interact with biological membranes and hydrophobic surfaces.[75, 76]

Polypropylene glycol (PPO) forms a central hydrophobic core in which methyl groups interact via van der Waal's forces when substances undergo solubilization.[77–80] However, water solubility results from hydrogen bonds resulting from ether-oxygen and water molecules in the PEO block, making Poloxamers readily soluble in nonpolar organic solvents and useful for the formulation of novel dosage forms[78, 81] as aqueous solutions of Poloxamers dissolved in acids, alkalis and metal ions.[78]

Pluronic F127 (PF-127) gels are particularly favored as cell and API carriers because of their non-toxic property, reversible gelation, high entrapment capability and ability to form gels at physiological conditions when used at relatively low concentrations.[82–84] At concentrations ≥20% w/w, PF-127 solutions are liquid at or below room temperature but transform into viscous hydrogels at body temperature (37°C). The controlled release of pilocarpine,[82] oxytocin,[84] mitomycin C[83] and vancomycin[85] have been achieved using PF-127 thermosensitive gels.

When coformulated with β-glycerophosphate, chitosan has also been used to produce thermosensitive hydrogels.[86–88] Han *et al.*[86] developed a formulation that exhibited a synergistic antitumour effect with doxorubicin and vaccinia virus vaccine expressing Sig/E7/LAMP-1 as a chemo-immunotherapeutic agent. Chitosan β-glycerophosphate thermo-sensitive hydrogels have similarly been developed for the delivery of ellagic acid and mitomycin C for the treatment of brain cancer[88] and bladder cancer,[89] respectively. In addition, chitosan hydrogels have been used for transcorneal administration of 5-fluorouracil.[87]

An incorporation of nanovesicles and gels is known as nanocomposite gels. These nanocomposite gels have successfully been used in the delivery of various drugs for transdermal purposes such as loading of papain in elastic niosomes gels for the treatment of scars,[70] encapsulating loperamide in liposomal gels,[90] formulating ketoconazole in niosomal gels[91] and retinoic acid and betamethasone in flexible liposomal gels.[31] Nanocomposite gels have been used to achieve a controlled and slow release of calcein superior to a pure hydrogel system.[92]

Thermosensitive polymeric systems avoid the use of toxic organic solvents. These materials can be used to deliver hydrophilic and lipophilic molecules with fewer systemic adverse effects while achieving targeted drug delivery with sustained-release attributes. Despite these benefits, several disadvantages associated with the use of these systems have been highlighted, which include an initial high-burst release, the low mechanical strength of gels resulting in possible dose-dumping, the absence of biocompatibility of polymers and a slow pH reduction of the system due to degradation in acidic environments.[73, 93]

pH-responsive hydrogels

The composition of all pH-sensitive polymers is consistent and comprises of acidic or basic functional groups. These groups can either accept or release a proton due to changes to the pH of the surrounding. Polymers with several ionizable groups or polyelectrolytes can be classified as weak polyacids or polybases. Weak polyacids are proton acceptors at low pH values and discharge protons at neutral and high pH.[94] Poly(acrylic acid) (PAAc) and poly(methacrylic acid) (PMAAc) are commonly used pH-responsive polyacids.[95, 96]

As the pH of the environment changes, acidic groups undergo ionization at a specific pH corresponding to the pK_a of the compound. The swift shift in the net charge of the connected group results in a change of the molecular structure of the polymeric chain, and the transition to an expanded state is facilitated by osmotic pressure from available mobile counter ions, neutralized by network charges.[97]

It is cardinal to select a polymer with a pH that matches a target pH range when devising a successful pH-sensitive system. As an initial consideration, the pK_a of the ionizable moieties in the polymer should possess the appropriate attributes for the intended application. To achieve specific adaptation, the pH of the selected polymer can be modified by various strategies,[98] such as copolymerization with other polyelectrolytes or incorporation of a hydrophobic moiety into the backbone of the polymer. Though homopolymers of many polyelectrolytes exhibit pH-sensitivity, pH-dependent polymeric systems result from copolymerization to achieve greater control of system behaviour for a specific delivery system.[98]

Chitosan is a polycationic biopolymer soluble in acidic solution. It undergoes phase separation in the pH range close to neutrality through loss of a proton on the primary amino functional group.[97] The gelation mechanism of chitosan occurs through electrostatic attraction between the ammonium functional group of chitosan and inorganic ions, hydrogen bonding between the chitosan chains or hydrophobic chitosan–chitosan interactions. Nonetheless, the resultant gel demands additional cross-linking to produce a gel of adequate mechanical strength to release low molecular weight API in a controlled manner. The porosity of the chitosan gel that forms, which is dependent on the crystalline state of the chitosan used, is mainly responsible for the structural strength of chitosan gels.[97]

Ion-responsive hydrogels

The unique properties, biocompatibility, accessibility and cost-effectiveness have led to the use of natural gums for many daily applications. This class of compounds includes polysaccharides such as gum ghatti, gum acacia, guar gum, gum tragacanth and konjac gum. Agar gum, alginates and carrageenans are derived from seaweeds, while gellan gum, xanthan gum, rhamsan gum and welan gum are derived from microorganisms. Gums were mainly used as additives for food products.[99–101] However, natural gums or their derivatives have been studied as excipients for pharmaceutical or biomedical reasons[102] or matrix tablet production.[103–107]

Dual-stimuli responsive hydrogels

Chitosan-based materials have frequently been utilized in drug delivery for extended/sustained release of therapeutic agents.[108–111] Particularly, chitosan-based injectable gels, when combined with glycerol, ethylene glycol and sorbitol, can deliver specific API at a target site.[112–114] The polyols maintain chitosan as a liquid, as they form a shield of water around the chitosan chains in an acidic solution to sustain its solubility at higher pH or at low temperatures.[109, 115] In addition, the use of β-glycerophosphate (β-GP) in combination with chitosan has been documented for applications in thermo-sensitive gel delivery.[116–118] Several interactions have been implicated during the gelation process, such as the loss of electrostatic repulsion and hydrogen bonding and increased hydrophobic interactions.

The increase in pH associated with the addition of β-GP to a solution of chitosan results in a reduction in electrostatic repulsion between chitosan chains. This promulgates an increment in interchain hydrogen bonding. Furthermore, increasing the temperature releases hydrogen bonds between water molecules and chitosan chains, permitting increased hydrophobic interactions between chitosan chains.[109, 117–119]

Drug delivery using micro- and nano-scale hydrogels has been successful due to the biocompatibility and flexibility of physicochemical properties in addition to the protection of API in harsh environments. The high water content of the hydrogels permits stealth activity and increased circulation time by avoiding detection and evasion of an immune response in the patient.[120–122] The delivery of antioxidants or sunscreens to melanocytes in deep skin tissues to protect effects against melanin and freckles production may be achieved using dual-stimuli pH- and temperature-sensitive liposomal gels.[123]

Ionic liquids

Ionic liquids (IL) are commonly defined as salts composed solely of ions, with a melting point below 100°C.[124, 125] The formation of IL from API that are salts has a long history, as liquid formulations avoid polymorphism present in crystalline forms and tend to promote dissolution into water, leading to higher bioavailability.[125] There has been an imperative requirement for novel scientific advances that generate pioneering and efficient drug therapies in recent years. The traditional strategies presently being pursued are attaining a stage at which it is challenging to develop new chemical entities that are efficacious. It is estimated that fewer than 10% of API currently evaluated in clinical trials attain market registration. This dramatically decreases the availability of effective medicaments for individuals in need.[126] Approximately 50% of all existing API are administered as salts. By pairing various counterions, it is possible to finely modify the physicochemical and biopharmaceutical properties of a given API. From a pharmaceutics perspective, the melting temperature and solubility are pertinent parameters from a drug processing and bioavailability point of view.[127]

Lipid phases have long been known to form within ionic liquids. One of the earliest reports of amphiphile self-assembly in ionic liquids is for βγ-distearoylphosphotidylcholine (DSPC) in ethylamonium nitrate (EAN), which forms a lamellar phase that shows similar transitions between ordered and gel phases as for DSPC in water.[128] Similarly, other lipids such as dipalmitoylphosphatidylethanolamine (DPPE) were shown to have a richer phase diagram in EAN than in

water. DPPE formed 2D hexagonal phases in the IL, which were not seen for DDPE in water until very high temperatures, due to binding of the IL increasing the area per lipid head group.[129] However, the formation of vesicles in IL is less often reported but has been noted for phospholipids[130] and glycolipids.[131] The lipid bilayer in the vesicle must remain sufficiently flexible to maintain the spherical shape. The melting temperature of lipids depends on chain length, saturation and interactions with the solvent. IL components with long hydrocarbon chains can insert into the bilayer membrane and lower T_m,[130, 132] but may also alter membrane fluidity, curvature and thickness, which may cause toxicity.[133]

Patra *et al*.[134] investigated the modulation of membrane properties by IL through monitoring the fluorescence of curcumin. Their research concluded that IL, which are extensively used in chemistry and have a bearing on human health, show a change in membrane properties. Long-chain IL resulted in a reduction in the phase transition temperature, and a higher molar ratio resulted in the fusion of solid-gel and liquid crystalline liposomal phases. Short chain IL had no significant influence on the phase transition temperature at molar ratios studied.[134]

Deep eutectic solvents

Deep eutectic solvents (DES) are a relatively novel solvents obtained by mixing organic compounds, resulting in a eutectic mixture. The melting point of the eutectic mixture is much lower than that of the individual constituents.[135] However, many liquids formed at non-eutectic ratios are also referred to as DES. DES have been anticipated as promising alternatives to orthodox IL as they overcome various limitations of IL. Specifically, natural DES, which consists of natural origin components, are promising as solvents and dispersants for pharmaceutical use because they are biodegradable, possess a low toxicity profile, and can dissolve a variety of distinct chemical compounds. They have been used to dissolve poorly water-soluble compounds such as griseofulvin, danazol, benzoic acid, itraconazole, AMG517, rutin, cinnamic acid and taxol. Similarly, they have found applications in dissolving macromolecules such as DNA, starch, chitin and proteins.[136–140] Interestingly, dissolution in DES can also stabilize API against hydrolysis compared to dissolution in aqueous solutions.[141] In DES and DES/water mixtures, API has been incorporated into microemulsions as a transdermal drug delivery system.[142] DES is also known to improve skin penetration for compounds dissolved in them.[143, 144] DES may also be formed where one or both of the components are themselves API,[145] avoiding polymorphism in solid-phase mixtures.

In the context of bilayer drug delivery, vesicle formation in DES has been noted for several phospholipids[146–148] and glycolipids. The chain melting temperature of lipids is generally increased in DES compared to that for lipids in vesicles in water. Still, it is also dependent on the hydrogen bond donor in the solvent.[147]

Conclusions

Topical drug delivery is a widely studied non-invasive route of administration. Topical drug delivery systems offer an appropriate and ideal alternative route of administration to the traditional oral route of administration for several reasons: evading hepatic first-pass metabolism, not requiring having a pleasant taste and circumventing gastrointestinal side effects. In addition, this drug delivery route allows for steady drug plasma concentrations, improved adherence to therapy, reduced frequency of administration and degradation in the gastrointestinal tract. It avoids the possibility of over or under-dosing. Several effective drug molecules are available for topical disorders. However, physicochemical properties and undesirable toxicity profiles have limited their therapeutic efficacy. Vesicular delivery systems have the potential to overcome these shortcomings due to their unique attributes such as high biocompatibility, simplicity of surface modification and suitability as vehicles for controlled delivery. However, incorporating these systems into environmentally responsive dispersants such as hydrogels, ionic liquids and deep eutectic solvents may enhance therapeutic prowess of these delivery systems. Consequently, improved vesicular drug delivery can be achieved by considering combining some of these formulation approaches.

Author Contributions

Conceptualization B.A.W.; writing-original draft preparation B.A.W., K.J.E., L.M.M., K.O.T., S.K.M., M.T.R.C., P.V.N. and P.A.M.; writing-review and editing B.A.W., P.V.N. and P.A.M.

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Conflict of Interest

None declared.

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