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REVIEW

Novel liquid-based approaches for transmucosal drug delivery

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Abstract Advancements in drug discovery, such as artificial intelligence, computational technology, and combinatorial chemistry, have led to numerous new promising drug candidates. However, most still fail to reach the market due to poor physicochemical properties, resulting in off-target or toxic effects. As a potential solution, non-invasive and targeted drug delivery at mucosal surfaces can deliver drugs directly to therapeutic sites to avoid off-target effects, decrease required drug doses, bypass hepatic first-pass metabolism, and circumvent uncontrolled drug release. Liquid-based drug delivery systems have advanced tremendously over recent years, with novel dosage forms such as ionic liquids, liquid crystals, stimuli-responsive phase transforming liquid systems, nanoemulsions, double-emulsions, self-emulsifying delivery systems, and eutectic systems being developed. These systems hold vast promise for transmucosal drug delivery as liquids generally provide superior spreadability compared to solid dosage forms, and some liquid systems provide prolonged mucosal retention times compared to conventional solutions. However, liquid dosage forms present regulatory challenges such as preservation, sterility, and stability requirements. This review discusses novel liquid-based formulation approaches to cross the ocular-, nasal-, oromucosal-, and vaginal mucosal barriers emphasizing advanced liquid drug delivery systems and the progress made toward clinical translation as a platform for future transmucosal liquid-based dosage form development.

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1. Introduction

The drug discovery process places immense focus on finding new lead molecules to treat various diseases[1]. Initially, drug discovery was a serendipity-based practice which evolved into a competitive modern science employing sophisticated technologies such as computer-aided design of drugs, combinatorial chemistry, establishing relationships between drug activity and molecular structure, high-throughput screening and artificial intelligence[1−4]. Despite these advanced technologies, safety, unfavorable physicochemical properties, poor membrane permeation, and insufficient therapeutic action frequently cause the elimination of drugs from further investigation during the final stages of clinical investigations[5]. This manifests a bottleneck effect impeding the translation of potent drug entities from clinical trials to the market as these compounds exhibit toxicities due to uncontrolled dosing or unfavorable off-target effects and low bioavailability[1,5,6]. This emphasizes that the therapeutic efficacy of highly promising drug entities is often hindered by insufficient and nonselective drug delivery[7]. Therefore, drug administration at specific locations for targeted delivery to reach therapeutic sites has gained increased scientific attention as a strategy to overcome uncontrolled systemic dosing, avoiding systemic toxic effects and reducing the dose needed for therapeutic efficacy while drastically decreasing side effect manifestation[7]. However, localized drug administration is a challenging field of drug delivery because vehicles or systems should be tailored to mediate the crossing of biological barriers[8,9].

Mucus is a distinct physical barrier to drug delivery across mucosal surfaces as it protectively covers the epithelia of drug administration sites such as the ophthalmic membranes, nasal cavity surfaces, oromucosal linings, and vaginal mucosal tissues[10]. Interestingly, the mechanical characteristics and chemical composition of mucus vary between different physiological sites as they perform different functions[11]. Additionally, chemical fluctuations like hormonal changes can also influence the structural and chemical capacity of mucus, implying that mucus is a constant yet evolving barrier to drug delivery[12,13]. Mucus can be described as a complex gel-resembling mixture harboring mucin proteins, lipids, cells, ions, pathogens, and immune components[1,13]. Due to the gel-resembling nature of mucus, liquid-based formulations have gained significant scientific attention attributed to advantages such as the ability to cover large surface areas, swift drug absorption, mucoadhesive properties, and reduced tissue irritancy potential when compared to solid formulations[14].

Conventionally, liquid dosage forms refer to a specific type of preparations used in the field of drug delivery where the drug is solubilized or dispersed in an appropriate liquid vehicle[15]. Examples include solutions, various types of emulsions, suspensions, elixirs, drops, tinctures, syrups, sprays, aromatic water, liniments, and aerosols[15,16]. These liquid dosage forms were reserved for aqueous soluble drugs with acceptable organoleptic properties and predominantly intended for administration in pediatric patients[15−17]. However, modern liquid-based drug delivery has evolved from emulsions to nanoemulsions, pickering emulsions stabilized by nanotechnology, multiple-emulsions, and innovative formulation techniques such as spontaneous or self-emulsification[18−22]. While ionic liquids, liquid crystals, and eutectic mixtures form part of a rapidly expanding field aimed at improving the aqueous solubility of drugs[23−25]. Therefore, liquid-based drug delivery can also provide a platform to optimize lipophilic drug delivery as the literature reports that 70%−90% of most newly created drug entities are inherently lipophilic[26−28].

Approximately 22% of marketed dosage forms are liquid-based with a significant expected increase within the near future due to the registration of numerous vaccines, drug−antibody conjugates, and monoclonal antibodies in liquid-type formulations[29−32]. Liquid formulations require detail-orientated design approaches to compensate for biopharmaceutical factors and physicochemical properties that do not present challenges in solid dosage forms such as preservatives and stabilizers[29,33]. This is of particular importance when considering localized transmucosal drug delivery from liquid-based drug delivery systems to facilitate the crossing of drug molecules across mucosal surfaces[34]. Additionally, liquid formulations intended for ophthalmic, intra-muscular, inhalation, or intranasal purposes should comply with specific sterility and stability requirements[29]. Liquid-based formulations have garnered significant scientific attention over the past decades with a clear interest in specific liquid-based drug delivery systems such as nanoemulsions, self-emulsifying drug delivery systems (SEDDSs), double-emulsions, stimuli-responsive liquid systems with sol-gel transition, ionic liquid-based systems, liquid crystals, and eutectic mixtures. Each of these liquid-based drug delivery systems holds unique advantages and limitations to crossing mucosal surfaces at different sites of administration as thoroughly considered by this review.

2. Mucosal barriers to drug delivery

2.1. The composition of mucus on surfaces at different physiological sites

The literature describes the mucus layer on biological surfaces as hosting the most immune cells of any bodily site and it functions as a barrier to the passage of xenobiotics such as drug molecules, pathogens, and foreign objects[35,36]. Mucus can be described as a viscoelastic fluid network maintained by mucus secretion from specialized goblet cells, submucosal glands, or secretory cells found in the underlying epithelia[37,38]. Mucus protectively coats organs and glands interacting with the external environment by trapping, degrading, and washing away pathogens or foreign objects while ensuring hydration and lubrication of mucosal surfaces[37,39,40]. Regarding structure, mucus presents a heterogenous matrix harboring mobile subunits that are loosely arranged relative to one another[41]. This is also broadly referred to as the macrostructure of mucus as particles, drugs, therapeutic carriers and pathogens exceeding 200 nm generally cannot traverse through the macrostructure to reach the underlying epithelia[41]. The microstructure of mucus refers to the mesh-like subunits established by mucin networks to entrap foreign substances. Due to the fine filtering capacity of mucin networks, the literature reports that nanocarriers between the range of 10−200 nm should theoretically be able to travel *via* channels within the mucin network[42,43]. Hence, larger particles utilizing the passages of the mucosal macrostructure to cross mucosal barriers can take longer to reach the underlying epithelia, exposing these particles to a higher risk of entrapment followed by expulsion during mucosal shedding[43]. However, Lai's group[43] have observed that utilizing relatively lower molecular weight chains of polyethylene glycol (PEG) to modify nanoparticles rendered permeation enhancement compared to unmodified nanoparticles. Their permeation experiments involving the crossing of cervical mucosal networks revealed that larger PEGylated nanoparticles (approximate diameter of 200 and 500 nm) displayed more rapid permeation than

smaller PEGylated nanoparticles (approximate diameter of 100 nm). Importantly, this study signifies that optimized physical properties such as droplet/particle size and tailored chemical characteristics like surface chemistry can facilitate the crossing of larger particles despite the reported mucin mesh size of 10−200 nm for cervical mucus[43].

Mucosal membranes exposed to the external environment, such as the ocular surfaces, nasal cavities, oromucosal region, and female reproductive tract, are considered promising physiological drug delivery sites due to advantages like targeted drug delivery[39]. Despite the filtering nature of mucus, which allows nutrient, gas, water, and hormonal exchange, the passage of most pathogenic organisms and drugs is restricted *via* adhesion and stearic barrier formation[39]. Mucus attains its biophysical and rheological properties from water as its main component, which accounts for up to 95% of its total weight[44]. Regardless of the mucosal site pathogens, lipids, proteins, salts, discarded cells, and macromolecules are entangled within the crosslinked, filter structure provided by mucins[38]. Importantly, the composition of mucus differs between mucosal surfaces located at divergent anatomical areas despite providing equivalent protection to the covered epithelium[11,39]. For instance, clearance of ocular mucus occurs every 5 to 10 min to remove potential irritants compared to the vaginal mucus lining that thins and thickens as governed by hormonal changes throughout the menstrual cycle[12,39]. The turnover rate for mucus production can be accelerated upon exposure to toxic substances or irritants to mediate successful removal[39]. Fig. 1 illustrates the mucosal layers on anatomical sites considered by this review, highlighting the complexity required for developing drug delivery systems for transmucosal drug delivery.

Apart from the unique composition of mucosal sites observed in Fig. 1, each mucosal surface forms part of an organ that performs different bodily functions and necessitates different physiological environments to optimally fulfil its protective capacity. As presented in Fig. 2, the mucosal clearance rate differs between anatomical and physiological sites and can significantly impact drug delivery, as this intrinsic dynamic process can hinder the crossing of drug particles to the underlying epithelia. As a rule of thumb, the mucosal turnover rate is linked to the thickness of mucus layers[38]. Hence, thicker mucus layers will generally present slower mucosal turnover rates to maintain the equilibrium between mucus shedding and secretion in preserving the efficacy of the mucosal barrier[45]. One should also bear in mind that the thickness of mucus can be influenced by diseases or as a response to irritant or toxin exposure to guard the underlying epithelia[46]. Generally, mucus unaffected by diseases or the environment can be described as either loose or firm mucus[38]. Loose mucus refers to mucosal surfaces of the respiratory tract, stomach, small intestine, and colon. Loose mucus is easily cleared by shear or suction mechanisms due to its fibrous composition, causing water retention and leading to thicker mucosal coatings[38]. On the other hand, firm mucus is a synonym for membrane-bound mucus. Membrane-bound mucus is not easily cleared by shear or suction mechanisms, as this mucus is anchored to the underlying tissue *via* a transmembrane domain to line mucosal surfaces of the eyes and nose[38]. Moreover, membrane-bound mucus harbors mucins comprising high molecular mass proteins of up to 40 MDa and mucin monomers of up to 0.5 MDa[35]. Membrane-bound mucosal barriers are capable of regulating the immune response as a responsive and dynamic physiological component closely affiliated with adaptive and innate immune reactions[47]. Due to its dynamic nature, mucus presents a formidable barrier to drug transport as influenced by physicochemical characteristics such as pH, ionic strength, charge, viscoelasticity, and pore size of different mucosal surfaces[13,37,44,46,48,49]. The literature reports numerous formulation strategies to tailor drug delivery vehicles to optimize mucosal barrier crossing *via* ocular-, -nasal-, -oromucosal-, and vaginal administration.

2.2. *Mucoadhesion as a means for drug molecules to cross mucosal barriers*

Mucoadhesion is a strategy that can be used to anchor a drug delivery vehicle to mucosal surfaces to achieve site-specific drug

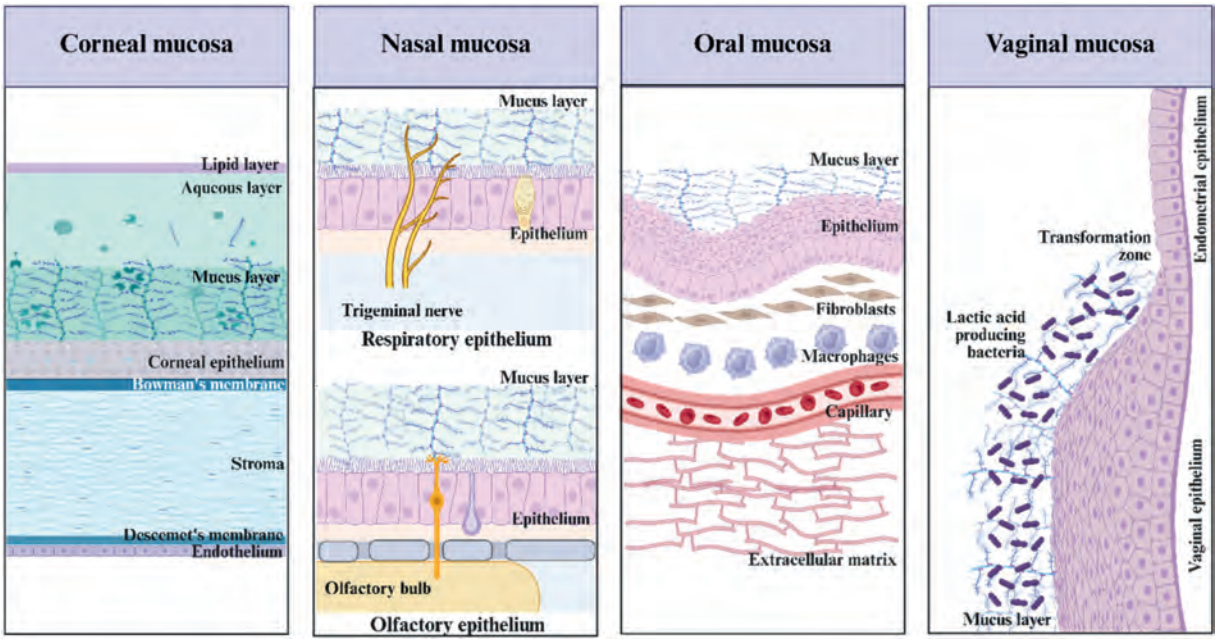

Figure 1 Visual representation of the corneal-, nasal-, oral-, and vaginal mucosa. Created with BioRender.

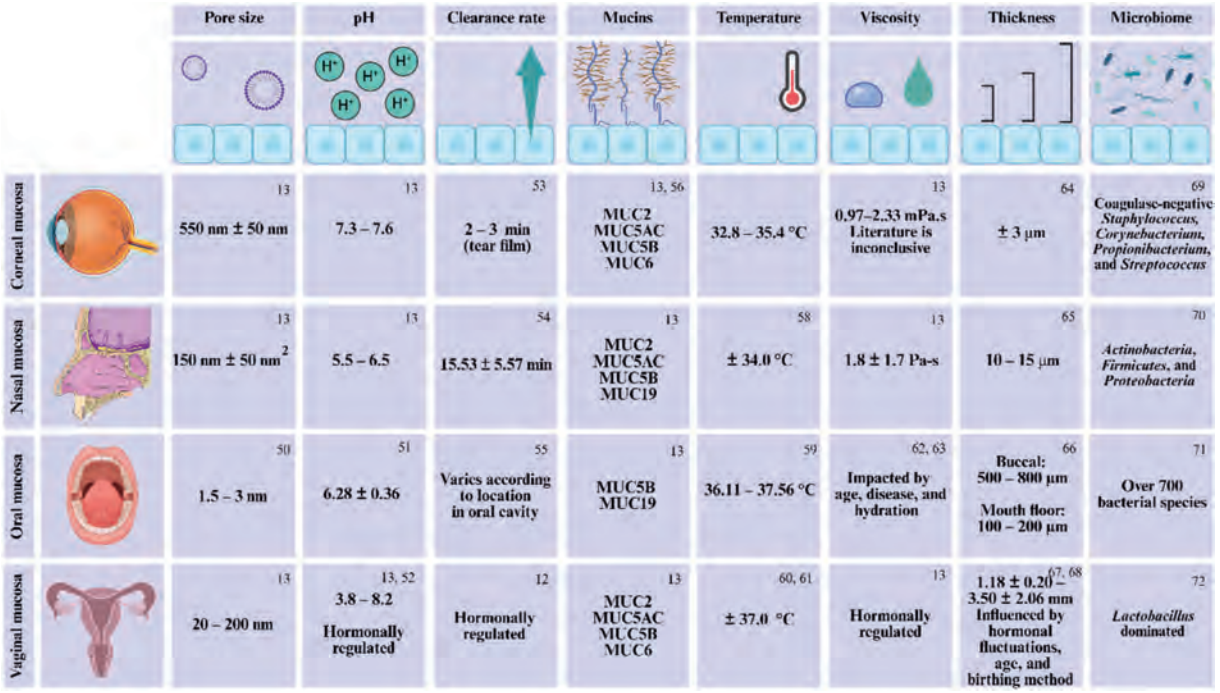

Figure 2 Comparison of the corneal-, nasal-, oral-, and vaginal mucosa[13,39,50–72]. Created with BioRender. Nasal mucosa image provided by Servier Medical Art (https://smart.servier.com/).

delivery[73]. Additionally, mucoadhesion prolongs contact time between mucosal surfaces and drug delivery vehicles to avoid mucosal clearance and thereby increase drug absorption[39]. Mucoadhesion is initiated during the contact stage of drug vehicle after administration by capitalizing on the repulsion or attraction facilitated between mucosal surfaces and drug delivery vehicles[74]. Importantly, during the application of liquid-based systems, this is also the stage where activation of lipid-based drug delivery systems like SEDDSs occurs based on the affinity of a liquid for mucus, as this will improve spreadability across mucosal surfaces to optimize mucoadhesion or mucosal penetration[74–76]. Improved spreadability and wetting are accompanied by enhanced swelling capacity of the mucus layer to allow increased access to the underlying epithelial surface[74].

Numerous theories are described in the literature to provide insight into mucoadhesive interactions between vehicles and mucus. The "Wettability Theory" considers wettability based on vehicle-mucus affinity during the contact stage[77,78]. Whereas the "Diffusion Theory" considers the sufficient interpenetration of excipients like polymers to mucin chains to mediate adhesive bonds of a semi-permanent nature during the consolidation stage[78]. According to the "Diffusion Theory", sufficient solubility of liquids in mucus combined with bioadhesive properties is highly favorable for mucoadhesion. Hence, the structural similarity of liquids to mucus enforces stronger mucoadhesive bonding[78]. As an additional option, the "Fracture Theory" describes the mechanical measurement of mucoadhesion by determining the force required to successfully separate two adhered surfaces. Importantly, despite the frequent use of the "Fracture Theory", it is only suitable for investigating the resistance to rupture of rigid- or semi-rigid agents, as it does not consider phenomena such as interpenetration of polymers[78]. The "Electronic Theory" considers mucosal adhesion as mediated by the transfer of electrons between the drug delivery vehicle and mucosal surfaces. Thereby, giving rise to a double-layer maintaining electrical charges between the mucosa and vehicle, leading to attractive force formation within the double-layer[78]. Lastly, the literature also considers the formation of primary and secondary surface binding interactions between drug delivery vehicles and mucus. Primary bonds are adhesions attributed to chemisorption by permanent covalent and ionic bond formation. Secondary bonds are considered more desirable due to their reversible binding capacity, such as van der Waals forces, hydrogen bonding, and hydrophobic interactions[78].

After considering the theories presented by the literature, it is important to acknowledge that these theories should be viewed as integrative processes at work to establish mucoadhesive interactions between vehicles and mucosal surfaces. For instance, wetting of the mucosal surface can be followed by excipient diffusion into mucosal structures to disrupt mucosal arrangement to allow adhesion or electronic transfer formation to optimize mucoadhesive drug delivery[78,79]. However, it is important to consider that mucoadhesive bond formation will differ between mucosal surfaces located at different anatomical areas (*i.e.*, rate of mucus turnover, the impact of hormonal changes on cervicovaginal mucus, and ocular tear film)[13,80–84], the nature of the incorporated mucoadhesive excipient in the drug delivery system vehicle (*i.e.*, molecular weight, flexibility, crosslinking density, charge, hydration capacity, hydrogen bonding, and concentration)[78,85–88], the type of liquid-based formulation[89,90], and the physiological environment that the vehicle will be exposed to after attachment (*i.e.*, mucosal immune response, nasal mucociliary clearance, bleeding during the menstrual cycle, and the effect of diseases on mucosal barriers)[78,91–95].

2.3. Muco-penetrating vehicles as a strategy for drug molecules to cross the mucus layer

Permeation enhancement strategies to cross mucosal barriers are based on the concept of temporarily reducing the viscosity, adhesion or elastic properties of the mucus layer to create a gateway for drugs into the underlying epithelia[96]. This can be achieved by inflicting dissociation of disulfide bonds, utilizing calcium chelators to counteract mucin compaction mediated by calcium, employing surfactants to impede hydrophobic cross-linking, or *via* mucus dilution mediated by osmolytes[46]. In terms of liquid-based formulations, the inclusion of hydrophilic agents like PEG, mucus-penetrating peptides, ligand conjugation, and mucolytic enzymes can improve mucus layer penetration[97]. However, rapid permeation into the underlying epithelia after mucus disruption is imperative since the mucus production rate will increase to repair the equilibrium between mucosal secretion and breakdown/removal[46]. The inclusion of mucus production regulators has been reported to improve penetration enhancement for absorptive mucosa[39]. As an example, niflimic acid, classified as a calcium-activated human chloride channel 1 inhibitor, has remarkably reduced mucus production within human airway mucosal cells[98]. However, in terms of transmucosal drug delivery, mucus production regulators have not been extensively explored.

Muco-permeative systems can be classified as either active or passive based on their penetrating mechanism. Passive systems aim to restrict interactions between vehicles and mucus by capitalizing on the slippery surface principle[41,99]. In the context of transmucosal drug delivery, a slippery surface vehicle refers to the ability of the vehicle to glide through mucus by minimizing adhesion to the mucus itself[41]. This mechanism can be described as similar to virus surface properties that mediate inert mucosal surface properties as attributed to increased density of anions and cations to facilitate gliding through mucus[45]. Additionally, PEG-based carriers render mucosal migration *via* the slippery surface principle[41]. In contrast to the inertness of passive systems, active systems participate in mucosal permeation by either changing the properties of the carrier upon mucus entrapment or by altering the properties of mucus. Zeta potential changing carriers are excellent examples of active systems that migrate through mucus by altering the pre-mucosal charge from negative to positive or even from negative to less negative to bypass mucosal entrapment in negatively charged mucus[41,75]. Zeta potential transitioning from negative to positive can be established by enzymatical cleavage targeting anionic surface-impeded substructures after arriving at the underlying epithelia to prevent reuptake into mucus while ensuring cellular absorption[41]. The latter group that renders active permeation *via* changing the three-dimensional mucosal structure generally refers to mucolytic enzyme decorated carrier systems that destroy peptide bond formation between glycoproteins or to carriers harboring free thiol groups intended for disulfide bond cleavage[41,79,100,101].

Due to the disruptive nature of muco-permeative systems, it is imperative to consider the impact of these systems on mucosal barrier integrity and local immune responses, especially upon chronic use. For instance, a drug delivery vehicle that irritates the nasal mucosa due to penetrative mucosal crossing mechanisms can render excellent permeation while inflicting compensatory hypersecretion, thereby disrupting the physiological balance[102]. This disruption can lead to epithelial barrier dysfunction, which can trigger unwanted immune responses and unpredictable drug delivery[102,103]. The implications of nasal mucosal barrier disruption are portrayed in Fig. 3.

Hence, it is important to trade off the advantages of rapid muco-penetration against unintended physiological responses, as these responses can negatively impact prolonged drug release at mucosal surfaces. Thereby, implying that in some cases mucoadhesion can be favored above muco-penetration as a less disruptive approach to cross mucosal barriers[38]. Some sources even consider combining these approaches as a potential solution to optimize mucosal drug delivery[38,116–118]. However, limited studies have explored or successfully implemented this combined approach.

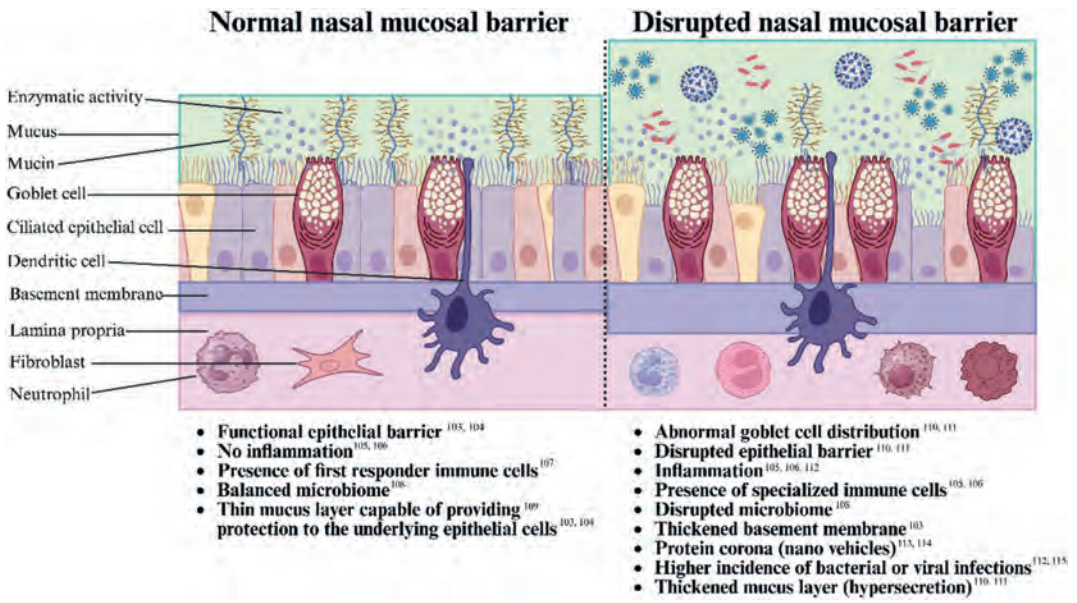

Figure 3 Schematic comparison of factors that influence drug delivery across normal and disrupted nasal mucosal barrier[103–115]. Created with BioRender.

3. Liquid-based drug delivery approaches

Liquids can be defined as the intermediate phase presenting features that coincide with gases and solids[119]. It is well-known that scientific knowledge gaps exist regarding the forces that govern structural liquid phase changes[119–121]. At some point, liquids were considered structurally homogenous vehicles[119]. However, the classic Bernal presentation of liquids as coherent, homogenous, and inherently irregular structures has evolved due to advances in visualization technologies (*i.e.*, electron microscopy, transmission electron microscopy, and scanning electron microscopy) to clarify experimental, computational, and theoretical discoveries describing liquid structures which is of specific interest to the nanoscale advances made regarding liquid-based drug delivery systems[122,123]. The advanced visualization techniques confirm that liquid systems present well-defined structures in the bulk phase and at liquid interfaces allowing accurate prediction of co-solvent and surfactant behavior during dosage form development[119]. In this section, the authors will consider the principles behind individual liquid-based drug delivery systems with an emphasis on the origin of these formulations, excipients that impart specific properties to liquid-based systems, biocompatibility considerations, and safety concerns.

3.1. Evolving emulsion development

Emulsions are considered an essential platform for drug delivery within the broader field of pharmaceutical sciences due to their vast applications in enteral, topical, vaccine, parenteral, and intravenous administration[124]. An emulsion is defined as a dispersion of two immiscible liquids[125]. The immiscibility of liquids is linked to their differing polarities. Generally, emulsions comprise an oil and water phase where one is dispersed in the other with the help of surfactants and co-surfactants. One phase is known as the continuous/external phase, which provides a liquid medium harboring droplets referred to as the dispersed/internal phase. Emulsions can be tailored to form water-in-oil (W/O), oil-in-water (O/W), oil-in-oil (O/O), or even multiple emulsions such as O/O/W, W/O/O, O/W/O or W/O/W by carefully selecting external and internal phases[21,124]. Apart from composition, emulsions are classified according to their droplet size (*i.e.*, nanoemulsions (<100 nm), miniemulsions (50–500 nm), microemulsions (10–200 nm), and macroemulsions (>0.1 μm))[124].

Confusion can arise from the droplet size categorization of emulsions, as some studies classify microemulsions as nanoemulsions due to the nano-sized droplets. Therefore, it is important to emphasize that nanoemulsions differ from microemulsions in terms of droplet morphology, thermodynamic stability, and production methods, which can be taken into consideration when intending to classify an emulsion correctly[126]. Nanoemulsions notoriously present as spherical droplets, whereas microemulsions can manifest droplets of spherical or irregular shapes. Importantly, nanoemulsions are thermodynamically unstable compared to microemulsions. This is attributed to the production method as nanoemulsions are prepared by high-energy procedures to enable minute droplet formation[126]. In contrast, microemulsions can self-assemble despite lower energy input, thereby rendering the formation of larger droplets. However, in the absence of high-energy production methods, microemulsions usually comprise higher surfactant concentrations to achieve emulsion stabilization, leading to concerns about their biocompatibility compared to nanoemulsions that can be stabilized by reduced surfactant concentrations[126]. Importantly, despite potentially lower surfactant concentrations, due to their small droplet size, nanoemulsions can portray superior membrane permeability eliciting a higher risk of toxicity[126,127]. Hence, it is recommended to reconcile microemulsions and nanoemulsions by considering each study individually according to the unique attributes of the emulsion and the mucus membrane target site to allow context-dependent and field-specific classification of nanoemulsions[126].

3.1.1. Nanoemulsions

The first peer-reviewed article referring to a nanoemulsion was published by Calvo and co-workers in 1996[128]. Interestingly, this specific nanoemulsion had a droplet size that exceeded 100 nm. According to the current definition of nanoemulsions, this first reported nanoemulsion would not be considered a nanoemulsion because they are now expected to exhibit droplet sizes smaller than 100 nm[129]. The surfactant phase in nanoemulsions must establish a sufficiently low interfacial tension between the oil and water phases to allow the formation of nanoscale droplets[130]. Due to the very small droplet size of nanoemulsions, they can cross mucosal membranes with more ease compared to microemulsions, which can render improved bioavailability.

Other advantages of nanoemulsions include high drug-loading capacity, solubilizing lipophilic drugs, improved *in vivo* stability, and superior bioavailability. Nanoemulsions also exhibit exceptional targeting capacity which is imperative during the administration of chemotherapeutic drugs to target tumors *via* site-specific release mechanisms and prolonged release to reduce the incidence of side effects. Site-specific release mechanisms refer to techniques like antibody conjugation, ligand attachment, and hyaluronic acid inclusion[131,132].

Surface modification of nanoemulsions also presents an attractive alternative to optimize drug delivery. As an example, the addition of cationic polymers can generate a positive surface charge on the negatively charged surface of phosphatidyl-serine-containing surfaces of tumor cells. In terms of transmucosal drug delivery, the addition of the polymer chitosan is an excellent example of a biodegradable, non-toxic cationic polymer reported to enhance transmucosal permeation *via* mucoadhesion established by electrostatic interactions with negatively charged mucus[133]. Chitosan has also been reported to optimize the targeting of the central nervous system following intranasal administration due to reduced mucociliary clearance and tight junction modulation of the olfactory epithelium[134]. Importantly, the lipid component of nanoemulsions is associated with increased biodegradability and tissue compatibility. However, surfactant choice and the concentration needed to generate nanoscale droplet formation can be seen as a potential drawback of nanoemulsions.

It is documented that more than 200 studies have investigated the toxicity of nanoemulsions and solid-lipid nanoparticles[135]. The overall conclusion was that nanoemulsion-inflicted toxicity was directly linked to the extent of surfactant interactions with cellular membranes instead of droplet size[135]. Therefore, non-ionic surfactants or polymer-surfactant combinations like pluronics, poloxamers, and polysorbates are considered non-cytotoxic and a favorable choice for nanoemulsions[135]. Some studies also reported that higher tolerability to surfactant exposure was observed when the surfactant was bound to nanoparticles compared to the free surfactant state of liquid systems[135]. Moreover, the literature has reported the negative impact of constant surfactant exposure on the gut microbiome, accompanied by inflammation[136]. Apart from surfactant inclusion mediating nanoscale droplet formation, the

formulation technique also contributes while researchers should consider how the technique can impact upscaling possibilities of nanoemulsions since droplet size reduction techniques can be a sluggish process[76,130]. Nanoemulsions can be produced by high-energy techniques such as high-pressure homogenization, ultrasonication, and microfluidization[130]. On the other hand, low-energy methods like solvent displacement/diffusion, phase inversion temperature technique, or self-emulsification can be used[130].

3.1.2. *Self-emulsifying drug delivery systems*

Colin W. Pouton first proposed the idea of SEDDSs in 1985 as a solution to oral lipophilic drug delivery despite the pioneering of spontaneous emulsions during the 1960s[137,138]. SEDDSs are isotropic mixtures comprising oils, water, and surfactants[76]. Generally, SEDDSs can be categorized according to droplet size, bioavailability, and stability[139]. When the predetermined oil and surfactant mixture is introduced to water nanoscale droplet formation can occur. The initial concept of SEDDSs was to present the drug in an oily concentrate, mostly protected by capsule inclusion to avoid exposure to gastric secretion. Then when the oily concentrate reaches the intestines the peristaltic movements and aqueous environment will mediate spontaneous emulsification[139]. Moreover, the scientific literature reports the utilization of SEDDSs for ophthalmic-, nasal-, oromucosal-, vaginal, and transdermal/topical drug administration[138,140–143]. SEDDSs intended for dermal application require adding the water phase as part of the formulation process as the oily concentrate will not be exposed to large fluid volumes as in the gastrointestinal tract and secretions like sebum and sweat drastically differ between individuals, implying that dermal SEDDS delivery cannot depend on secretions to provide an aqueous self-emulsifying environment[144]. On the other hand, SEDDSs intended for transmucosal drug administration should exhibit mucoadhesive-, mucopenetrating, or a combination of these properties to avoid clearance from mucosal sites while establishing cellular uptake[22,75,76,142,145–147]. Rapid emulsification within small fluid volumes is also essential as the rate-limiting step for delivery of SEDDSs is the completion of spontaneous emulsification before the mucosal barriers can be crossed[21].

A recent study investigating enhanced oil recovery in the petroleum industry, where self-emulsification is preferred over high-energy emulsification methods, confirmed that spontaneous emulsification is influenced by the pH of liquids[148]. The results presented by Liu's group[148] confirm that a low pH value is associated with an increased tendency toward spontaneous emulsification. Thereby, implying that the natural pH of the specific transmucosal drug administration route can impact spontaneous emulsification. Moreover, spontaneous emulsification is governed by surfactant structure as well as concentration, oil-water phase composition, the addition of non-aqueous solvents, the inclusion of co-surfactants, and the order of excipient addition[148–150].

Apart from surfactant structure and concentration, the ratio of oil to water phase, adding non-polar solvents and/or co-surfactants, solution salinity, and temperature can influence spontaneous emulsification. Importantly, lower oil-to-surfactant ratios have been reported to advance spontaneous emulsification. In addition, elevated surfactant concentrations can cause tissue irritation or microbiome disruption[151]. Ideally, spontaneous emulsification should be facilitated by the lowest possible surfactant concentration. Surfactant concentration also influences droplet size. Monitoring droplet size change over time and measuring the polydispersity index (PDI) of SEDDSs is imperative to predict ease of spontaneous emulsification, rate of successful drug release, and transport across mucosal membranes[152].

Excipient choice also impacts the class of SEDDS that are produced. For instance, the inclusion of long-chain triglycerides renders the formation of a conventional SEDDS. Whereas medium- and short-chain triglyceride inclusion can give rise to self-micro-emulsifying drug delivery systems (SMEDDSs) with a droplet size range of 100−250 nm and self-nano-emulsifying drug delivery systems (SNEDDSs) formation with a droplet size $<$100 nm. Some sources differentiate between SEDDSs and SMEDDSs due to the translucent nature of SMEDDSs compared to SMEDDSs. However, all sources do not differentiate and often use these terms interchangeably[153]. The formation of SMEDDSs and SNEDDSs can be mediated by surfactants possessing elevated hydrophilic-lipophilic balance (HLB) values combined with certain co-surfactants to improve bioavailability and emulsion stability[139]. SEDDSs improve drug bioavailability by presenting solubilized lipophilic drugs to reduce dissolution rates at absorption sites. Therefore, rapid spontaneous emulsification in small physiological fluid volumes can render nanosized droplet formation at mucosal surfaces to enhance drug absorption. Small droplet formation provides a large interfacial surface, allowing drugs to migrate from the lipid phase to the aqueous physiological environment. Additionally, encapsulation provided by SEDDSs can guard against enzymatic drug degradation and tissue irritation due to drug shielding in small oil droplets[154].

3.1.3. *Double-emulsions*

Multiple emulsions are a class of liquid-based dosage forms with endless pharmaceutical applications due to their liquid-in-liquid-in-liquid configuration, leading to them being described as emulsions of emulsions. These emulsions differ from conventional emulsions due to the presence of an additional dispersed phase to fulfil the role of a continuous phase. At this stage, double-emulsions are the most explored class of multiple-emulsions in the pharmaceutical sciences. William Seifriz[155] was the first author to report research works evaluating the properties of double-emulsions by considering the impact of oil phase density on the class of emulsion formed in 1925. Advanced visualization techniques have confirmed the formation of numerous classes of double-emulsions such as O/W/O, W/O/W, O/O/W, O/W/W, and W/O/O. In order to stabilize double-emulsions, more than one surfactant should be included to maintain emulsion stability due to the thermodynamic instability at two interfaces, in contrast to the single unstable interface present in conventional emulsions[156]. The literature recommends that a surfactant with a high HLB value and a surfactant with a low HLB value should be included to stabilize double-emulsions. Thereby, presenting a strong contrast compared to the formulation of general emulsions stabilized by either one surfactant or a combination of surfactants to establish W/O or O/W emulsion formation based on the facilitated HLB value[156]. Double-emulsions present numerous drug delivery possibilities as both lipophilic and hydrophilic drugs and stimuli-responsive polymers can be included[157,158]. This also implies that co-solvent inclusion can be unnecessary since both an oil and water phase are present for drug and excipient solubilization. Similar to general emulsions, double-emulsions also guard drugs against enzymatic degradation while mediating controlled drug release upon mucosal surface application[159]. From a cost-effective perspective, double-emulsions harboring two water phases can be more affordable to produce compared to general emulsions, as the

lipid content of these double-emulsions is reduced compared to classic O/W emulsions[159].

Double-emulsions can also be prepared by spontaneous emulsification if excipient selection is optimized during pre-formulation studies. This involves the preparation of a primary emulsion which is then subjected to the addition of an external phase without any excessive stirring or heat application. A recent publication by van Staden and co-workers[21] reported capturing the mechanism of spontaneous nano double emulsification for the first time with transmission electron microscopy, as presented in Fig. 4. The authors reported an average droplet size of 92.46 ± 5.52 nm with a PDI of 0.391 ± 0.05. However, upon transmission electron microscopy imaging, it was discovered that even smaller droplets were harbored within the larger droplets. Thereby, signifying that the dispersed droplets were smaller than 92.46 nm as dynamic light scattering could only detect the larger droplets. These W/O/O nano self-double emulsifying drug delivery systems also report the first double-emulsion intended to incorporate four drugs with strikingly different physicochemical properties[21]. Sustained release of drugs from double-emulsions has been reported[160]. However, the study by van Staden and co-workers did not include drug release studies to confirm the sustained release of the four anti-tubercular drugs intended to provide a supplementary treatment option for cutaneous tuberculosis.

3.2. Phase transforming liquid formulations

Drug delivery systems intended for site-specific administration should control drug release and absorption within the *in vivo* situation, while maintaining physical stability during storage periods[161]. Stimuli-responsive liquid-based drug delivery systems have garnered significant scientific attention since the 1950s after a study by Kuhn and co-workers pioneered the use of smart polymers[162]. As an example, the physical phase of such vehicles transforms from a solution to a gel or a gel to a solution once exposed to the expected stimulus (*e.g.* a specific physiological condition) of the targeted site or if a type of external force is applied to the dosage form. External stimuli of either a chemical or physical nature can generate a rapid response by these vehicles, leading to reversible macroscopic changes during phase transitions[163]. Chemical triggers for phase transition include pH, enzyme exposure, redox potential, and ionic factors. Physical triggers used to modulate phase transition are light exposure, temperature changes, magnetic- or electric field application, and mechanical stress[163,164]. Phase transitional changes are facilitated by polymers described in the literature as intelligent, smart, stimuli-responsive, or environmentally sensitive, attributed to altered molecular interactions following stimuli exposure[163,164].

As the first example, thermo-responsive polymers can be acquired from polymers exhibiting neutral amphiphilic properties like hydrophilic amide carriers, acrylics, or alcohol groups, together with hydrocarbon backbone chains known for their hydrophobicity[165]. In terms of temperature-mediated phase transition, stimuli-responsive polymers undergo a coil-to-globule transformation[166]. Generally, this transformation is established by the presence of hydrophilic- and hydrophobic functional units that transition from a hydrated to a dehydrated state, rendering a phase transformation from a homogenously dissolved solution to a gel-resembling heterogenous biphasic state due to minute temperature changes[165]. The literature also reports that the phase transition of polymer-solvent vehicles can be influenced by hydrophobic interactions and hydrogel within the system if exposed to temperatures exceeding the critical solution temperature[167,168]. At first, the hydrophilic groups of polymers harbored in a homogenous monophasic system swiftly interact with water molecules of mucosal surfaces, rendering the formation of hydrogen bonds to produce hydrated coils occupying random shapes. Upon exposure to temperature changes, hydrophilic functionalities are isolated from water implying that water molecules can no longer gain access to hydrophilic functionalities. This phenomenon initiates polymer re-crystallization presenting nonhomogeneous systems due to dehydration and biphasic transition[165].

Apart from the phase transitions presented in Fig. 5, polymer shape disruption and structure shrinkage facilitate drug release. Hence, it is important to distinguish between the two types of polymer solutions described as lower critical solution and upper critical solution polymeric solutions. Lower critical solution polymeric solutions (*i.e.*, entropy-driven systems) are preferably

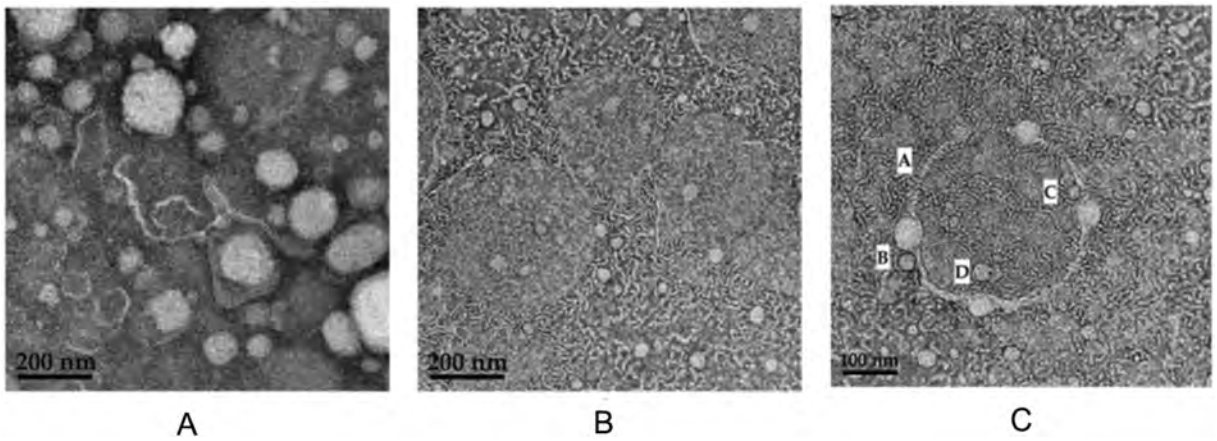

Figure 4 Transmission electron microscopy (TEM) images for (a) primary emulsion (9:9:2) comprising water to internal oil phase to surfactant phase; (b) Self-double-emulsifying drug delivery system (SDEDDS) (9:9:5) containing water to internal oil phase and surfactant phase (9:2) to external oil phase. (c)TEM image of the mechanism of self-double emulsificationwhere the surfactant phase establishes (A) the formation of a membrane structure; (B, C) and then water is surrounded by the surfactant phase leading to small droplet formation in the internal oil phase, and. (D) Demonstrates the presence of smaller droplets inside the larger droplet. Reprinted with permission from Ref. 21. Copyright © 2023 MDPI.

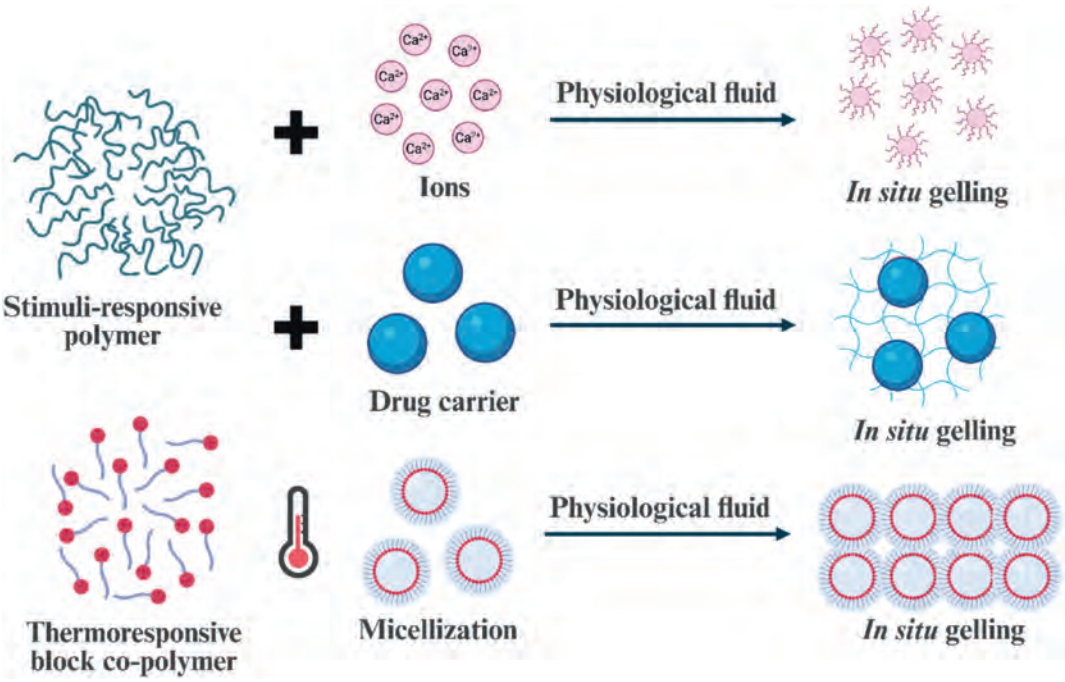

Figure 5 *In situ* gelling transition of stimuli-responsive polymers. Created with BioRender.

used over upper critical polymeric solutions (*i.e.*, enthalpy-driven systems) for phase transitioning liquid systems, as lower critical solutions have a limiting temperature where a binary phase transition occurs and hydrophobic interactions dominate[165]. This is also described as "negative thermosensitive polymers" in contrast to "positive thermosensitive polymers" that require cooling before phase transition can occur[165]. Importantly, thermo-responsive polymers are generally described as highly biocompatible and biodegradable, which is imperative for transmucosal drug delivery, where irritation at sensitive epithelial sites and microbiome preservation should always be considered[169]. Moreover, polymer selection should render permeation enhancement by considering characteristics imparted by polymers such as mucoadhesion, drug release behavior, and viscosity[170]. The literature also debates the importance of favoring natural polymers (*i.e.*, pectin, chitosan, gellan gum, and xyloglucan) that exhibit *in situ* gelation above synthetic polymers (*i.e.*, poloxamers (P407 and P188) and Carbopol) due to biocompatibility. However, it should also be considered that natural polymers generally require more than one stimulus to undergo *in situ* gelation compared to synthetic polymers that only necessitate one stimulus to establish phase transition. Thereby, implying that synthetic polymer inclusion can simplify dosage form development as mucosal surfaces can drastically differ in terms of pH and even temperature, and considering both factors can impede successful *in situ* gelation development[170]

Apart from polymer selection, researchers can consider physical and chemical crosslinking techniques to establish *in situ* gelation. Physical methods such as phase transition mediated by pH, temperature, or ionic mediation are preferred due to reduced mucosal irritation risk and simplified formulation techniques[170]. Chemical crosslinking techniques involve the addition of additional excipients, apart from polymers, to enable *in situ* gelation, such as organic solvents and co-crosslinkers, which can cause mucosal irritation. An interesting example is provided by photopolymerization, producing *in situ* gelation *via* an exothermic reaction occurring during polymerization rendering heat generation potentially inflicting mucosal irritation[170].

3.2.1. *Sol-gel transition dosage forms*

Regarding transmucosal drug delivery, applying gels initially presented as a solution with a planned stimuli-mediated phase transition can allow simplified handling before and during administration. On the other hand, stimuli-responsive phase transition allows increased retention time at mucosal surfaces to improve epithelial drug absorption[170]. Stimuli-responsive polymers display pseudo-plastic rheologic behavior, implying that these excipients will improve the spreadability of sol-gel formulations across mucosal surfaces[171]. During the application of sol-gel formulations, solution viscosity is reduced as the force of application re-aligns entwined polymeric chains towards the direction of shear applied. Upon introduction to the specific conditions of the physiological environment, the original rheologic properties are re-established to mediate the formation of a viscous gel. In terms of localized, transmucosal drug delivery converting rheological properties to their original form implies that sol-gel formulations can avoid formulation leakage from body cavities like the vaginal channel and impeding mucociliary clearance from the nasal cavity[170,171]. Thereby, allowing prolonged contact time between mucosal surfaces and liquid drug delivery systems to govern controlled and sustained drug release for localized or systemic therapeutic effects[171].

3.2.2. *Fluid gels*

Fluid gels, also named shear gels, describe the suspension of gel particles in a continuous liquid phase. Shear application or physical disruption of a biopolymer solution during the cooling phase of the gelation process is known to produce fluid gels[172]. Thus, rendering paste or fluid resembling properties by fine gel formulations to exist as highly concentration gels suspended in a

liquid matrix. Interestingly, fluid gels and quiescent gels can have identical chemical compositions, but different drug release behavior due to the altered physical properties[172,173]. Drug delivery from fluid gels can be optimized by exercising control over cooling and fluid rates. Additionally, the concentration and type of biopolymer selected during preformulation can also impact fluid gel properties. Fluid gels exhibit thixotropic behavior upon substantial yield stress application signifying that fluid gels can be applied as gels, but exhibit phase transition by returning to a fluid upon increased shear application followed by recovering to its fluid gel state following force removal[174,175]. This is of particular importance in transmucosal drug delivery as fluid gels can be easily administered with devices by transpiring into a liquid phase to cover larger mucosal surface areas by spraying devices and then remarkably return to a fluid gel state to promote mucosal surface retention time and improve permeation enhancement. In contrast to delivery in body cavities, fluid gels present the option of drop administration on the corneal surface followed by the visco-elastic gelling of the drops to increase retention time[176]. Interestingly, the literature reports that fluid gels can be employed as an emulsion encapsulating vehicle, replace the lipid component of emulsions, and mediate foam stabilization[177,178]. Moreover, fluid gels swiftly regain their fluid gel consistency after shaking and are known for superior stability properties[175].

3.3. Ionic liquid-based drug delivery systems

3.3.1. Ionic liquids

Ethyl ammonium nitrate was reported by Paul Walden as the first discovered ionic liquid in 1947[179]. Despite approximately a century of ionic liquid research, a real interest in ionic liquids only emerged during the past two decades[180]. Ionic liquids are a molten salt class harboring cations provided by an organic source and anions from an organic or inorganic source at a low temperature ($<100\ ^{\circ}C$). Ionic liquids possess unique physicochemical properties such as high conductivity, superior chemical and thermal stability properties, and minimal vapor pressure, signifying their clear difference from conventionally used solvents and salts[14]. Due to their unique properties, ionic liquids can be used to fulfil the water or oil phase role of liquid vehicles. Moreover, ionic liquids can also be used as structural components to mediate the formation of micelles, microparticles, nanoparticles, and emulsions[181]. According to the macrocyclic structure of ionic liquids, these liquids can generally be divided into four primary groups (*i.e.*, *N*-alkyl-pyridinium, phosphonium, alkyl-ammonium cations, dialkyl-imidazolium)[181]. Apart from their macrocyclic structure, ionic liquids can also be distinguished based on their chronological order describing their discovery providing three generations of ionic liquids.

The first generation of ionic liquids comprises cations paired with halide anions. These liquids are known for low melting points, superior thermal stability, and retaining their liquid form upon exposure to a broad temperature range. First-generation ionic liquids are expensive to produce and prone to participating in oxidation and hydrolysis reactions[181]. On the other hand, cations for second-generation ionic liquids are provided by dialkylimidazolium, alkyl-pyridinium, ammonium, and phosphonium with anions obtained from tetra-fluoroborate and hexa-fluorophosphate inclusion. Second-generation ionic liquids are less susceptible to oxidation and hydrolysis. The second-generation ionic liquids also expanded the customization of ionic liquids to alter properties such as thermal stability, solubility, biodegradability, viscosity, melting point, and hydrophobicity to obtain ideal physicochemical properties for unique purposes[181]. Hence, the second-generation ionic liquids evolved into third-generation ionic liquids often used in green chemistry to produce ionic liquids to perform a specific function[181−183]. Due to the involvement of green chemistry, anions are provided by natural sources like fatty acids and amino acids while cations are mainly obtained from choline to mediate transmucosal drug delivery[14].

Choline-based ionic liquids are known to improve mucoadhesion by shielding mucin glycoproteins. The isolation of negative mucin domains leads to a reduced mucosal viscosity without causing structural damage to mediate mucosal permeation[184]. The biological origin of third-generation ionic liquids allows physical strength impediment of mucus by altering the viscosity and elasticity of the mucosal layer to enable the epithelial crossing of drugs. The increased viscosity of ionic liquids not only guides mucosal modulation but also prolongs contact time between mucosal surfaces and ionic liquid-based carriers[73]. Pairing choline with appropriate anions can also advance mucosal modulation by tailoring the pH and conductivity of liquid formulations[73]. Ionic liquids can also enhance the solubilization of polymers to furnish vehicles with additional mucoadhesive properties allowing controlled drug release[185]. Moreover, innovative dosage forms like ionogels have also been produced *via* the incorporation of ionic liquids[185]. Ionogels are described as combining an ionic liquid and a solid continuous phase. These systems can be classified as inorganic, organic, or hybrid inorganic−organic systems as defined by their synthetic route[181]. Another advantage of ionic liquids is the inherent antibacterial and antifungal capacity provided by anionic groups[73]. Moreover, drug release within divergent pH environments can be controlled *via* ionic liquid inclusion. Drugs or drug combinations can also be converted into ionic liquids to expertly modulate their physicochemical properties by eliminating the possibility of polymorphism, enhancing aqueous solubility, improving thermal stability, and tailoring dissolution rates[186]. Moreover, as demonstrated by Fig. 6, ionic liquids can be encapsulated *via* solvent evaporation, interfacial polymerization, impregnation, and emulsion polymerization[187].

The development of ionic liquids and their applications have surpassed toxicity evaluations as ionic liquids are often branded as "green solvents" generating the misconceived perception that all ionic liquids are safe[188]. The literature reports that increased cation alkyl chain length holds a higher risk of toxicity[188−190]. The mechanism of toxicity is based on alkyl chain insertion, ultimately impeding cellular membrane formation and inflicting apoptosis. Therefore, increased alkyl chain polarity can restrict their capacity to participate in hydrophobic interactions regarding cellular membranes[188]. Another possibility includes zwitterionization, where an anionic moiety is inserted at the final section of the cationic alkyl chain[188,191]. Alternatively, bionic liquids such as choline cations are employed to reduce toxicity profiles[188]. As a metabolite of the neurotransmitter acetylcholine and the presence of phosphatidylcholine as a cellular membrane polar head group, choline is considered less toxic compared to the initial cationic sources of ionic liquids. Research also revealed that choline ionic liquids paired with anions provided by acetate, aspartate, chloride, and glutamate produce safer toxicity profiles. Therefore, the selection of the anionic source is imperative when producing choline-based ionic liquids[188].

3.3.2. Liquid crystals

An Austrian botanical physiologist, Friedrich Reinitzer, discovered the liquid crystal phase in 1888. Reinitzer reported two

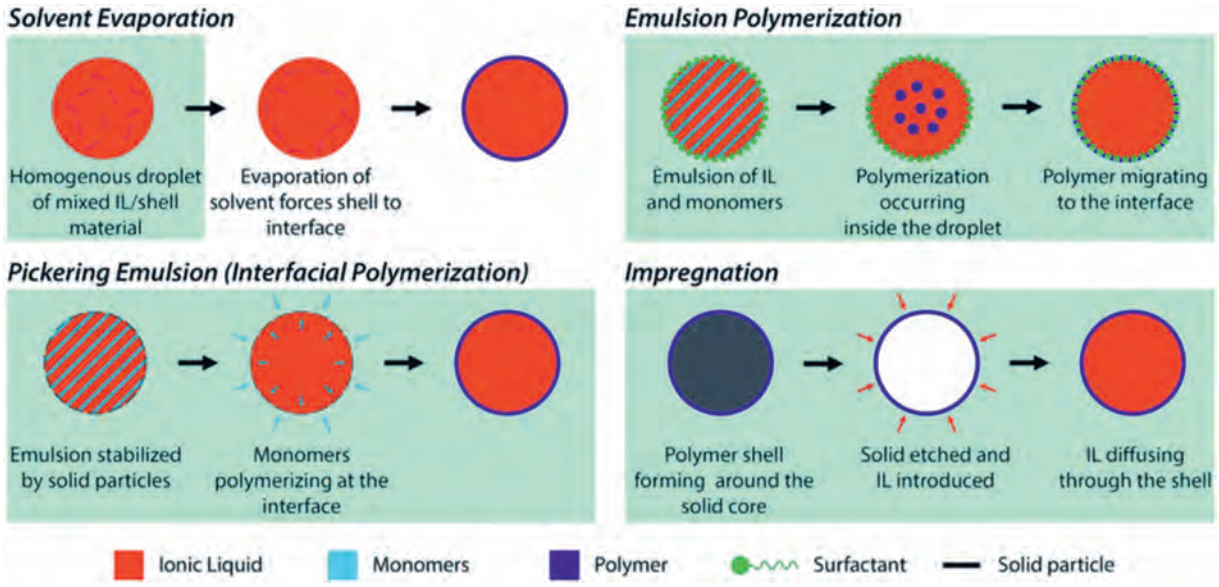

Figure 6 Schematic representations of the different methods used for the preparation of encapsulated ionic liquids. Reprinted with the permission from Ref. 187. Copyright © 2021 American Chemical Society.

melting points for cholesteryl benzoate that he successfully extracted from the root of a carrot[192,193]. He observed that the solid form of cholesteryl benzoate at 145 °C transpired into a turbid liquid and became transparent at a temperature of 178.5 °C. Thereby, discovering the transition from the solid phase to liquid crystal formation followed by its metamorphosis to the liquid phase[194]. These liquid systems simultaneously combine solid and liquid state characteristics by generating a mesomorphic state[195,196]. In this mesomorphic state, the solid can be described as positively disordered to generate properties such as electrical and optical anisotropy. While the liquid is considered orientally ordered to provide mobility comparable to fluids. Liquid crystalline systems are biocompatible, stable systems that can be prepared cost-effectively to improve aqueous solubility and control the rate of drug release. Additionally, liquid crystalline systems can increase drug potency and therefore enhance pharmacological effects[195]. The mesomorphic state can be classified as thermotropic liquid crystals or lyotropic liquid crystals. Thermotropic liquid crystal formation is temperature-dependent and subdivided into cholesteric, nematic, and smectic liquid crystal systems. On the other hand, lyotropic liquid crystals are produced *via* the liquefication of a drug in numerous solvents[195].

These systems comprise self-assembled amphiphilic molecules generating structures such as cubic, hexagonal, and lamellar mesophases. Regarding drug delivery lyotropic liquid crystals have garnered significant scientific attention as a tailorable drug delivery carrier as the liquid crystallinity of lyotropic liquid crystals is a function of solvent concentration[196]. Lyotropic is derived from lyo indicating "solvent" and tropic is a synonym for "forms" signifying that lyotropic refers to solvent formation. This is attributed to the self-assembling capacity of lyotropic systems as influenced by the concentration-dependent addition of solvents. As a one-dimensional type of lyotropic system, lamellar phases comprise amphiphilic molecule bilayers, thereby separating water and oil phases[197]. Hence, interactions between water and oil are prohibited which can improve drug encapsulation. Moreover, bilayer thickness can be controlled by considering the partitioning between different oil phases and water as well as water or drug concentrations present in the liquid crystalline system. As the second type of lyotropic system, hexagonal liquid crystals refer to surfactant-generated micelles transpiring into advanced cylindrical micelles[196]. Aggregation of these cylindrical micelles then facilitates two-dimensional higher-order structures known as the hexagonal phase. The water phase concentration can impact the formation of reverse hexagonal phase or general hexagonal phase formation, similar to the formation of reversed micelles in oil-rich formulations compared to general micelle formation in water-rich formulations[196]. Interestingly, polarized light microscopy investigation of hexagonal liquid crystals described a fan-resembling structure. The fan-resembling structure is mediated by the hexagonal arrangement of each cylindrical micelle encircled by six additional cylindrical micelles, where the radius of the divided cross-section is related to the molecular length of the incorporated surfactant[198]. Hence, providing a favorable structure to maintain *in vivo* stability, enhancing drug loading, and advancing the delivery of macromolecules. The third type of lyotropic system, known as cubic liquid crystals, refers to crystals formed by a lipid bilayer, with an approximate thickness of 3.5 nm, continuously curving to create channels that avoid aqueous contact[196]. Thereby, generating a large interfacial area of approximately 400 m^2/g. This liquid crystalline phase is hallmarked as a more rigid structure able to optimize drug release while presenting exceptional drug loading capacity. Moreover, different cubic liquid crystalline phases (*i.e.*, double diamond-, body-orientated-, and gyroid lattice cubic phase) are considered more resistant to instability upon dilution compared to other liquid crystalline phases. However, cubic phases are considered more suitable for lipid drug delivery due to a reduced water presence[196]. The multi-dimensional structures of the different lyotropic liquid crystalline phases are presented in Fig. 7[197].

Apart from the multi-dimensional structures of liquid crystalline drug delivery structures, the storage stability of liquid crystals remains imperative as these systems are influenced by pH and temperature changes[197]. Normal liquid crystal storage conditions specified at 4 °C where the transition of liquid crystals upon storage has been reported[197,199]. Emulsions harboring lyotropic liquid crystals have been reported to maintain stability for a 1-year

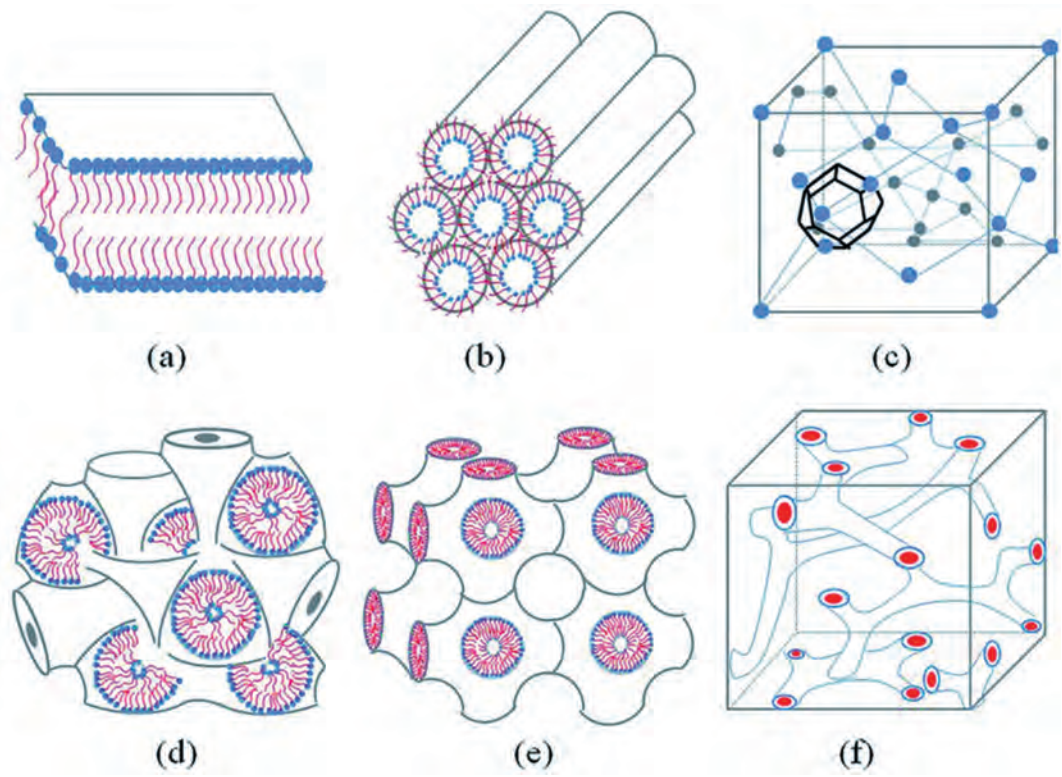

Figure 7 Schematic representation of the lyotropic liquid crystalline phases commonly found in neutral lipid/water systems. (a) Lamellar phase (b) reverse hexagonal phase (c) reversed micellar cubic (d) reversed bicontinuous cubic (e) reversed bicontinuous cubic (f) reversed bicontinuous cubic. Reprinted with permission from Ref. 197. Copyright © 2018 American Chemical Society.

storage period with an expected structure decomposition following 18 months of storage[199]. A study has demonstrated that storage times of hexasomes generated by liquid crystalline systems can be lengthened in decreased pH conditions[196,200]. Another challenge accompanying drug delivery from liquid crystalline systems is the initial rapid drug release that can lead to either systemic or local toxicity depending on the route of administration[196,201]. Generally, rapid drug release is overcome *via* structural drug modification[196]. Additionally, the introduction of alkyl chain linkage in the liquid crystalline structures can prolong drug release[196]. Regarding toxicity, the excessive use of surfactants, co-surfactants and liquid crystalline systems as a combination presents a higher risk for toxicity[196]. However, surfactants are essential components of these systems to improve drug loading capacity. As a potential solution, the literature reports that the inclusion of amphiphilic lipids of a biodegradable and biocompatible nature can potentially decrease the incidence of toxicity[196].

3.3.3. Eutectic systems

Frederick Guthrie named the first eutectic system eutēxia, a Greek word meaning "well-melting", in 1884[202,203]. Eutectics are notoriously used by various industries with each field naming eutectics differently. Within the thermal energy field, eutectics are known as phase change materials, the metallurgy industry refers to eutectic alloys, green chemistry practices investigate deep eutectic solvents and low transition temperature mixtures, and the pharmaceutical sciences refer to eutectic mixtures[203]. Eutectic mixtures present a lower melting point for a homogenous mixture of solids compared to the melting point of individual solid components added in a specific molar ratio as attributed to non-covalent interactions[202]. Eutectic systems provide an alternative option for enhancing the aqueous solubility of drugs. Deep eutectic systems are a modern version of eutectic systems that pertain to an advanced melting point depression capacity known for not only lowering the melting point of the mixture to a lower melting point than individual components, but to a melting point lower than room temperature[204]. The literature describes deep eutectic systems as analogous to ionic liquids as both liquid-based vehicles can be classed as designer solvents with minimal vapor pressure[205]. However, deep eutectic systems are considered more cost-effective and require simplified preparation techniques while potentially being less toxic than ionic liquids[206].

Interestingly, deep eutectic mixtures have superior thermodynamic stability compared to amorphous drug delivery systems[204]. Eutectic systems are established on the principle of size or shape mismatching between components mediated by weak adhesive interactions between materials of a non-isomorphous nature, rendering similar packing patterns and lattice arrangements to those of parent molecules. Thermodynamically speaking, eutectics can form upon a greater entropy gain compared to an enthalpy gain during molecular ordering. The equilibrium between entropy and enthalpy partially depends on the structure of parent molecules. Additionally, close contact between potential eutectic-forming solid components should be paired with the ability of these components to present mutual solubility when presented in their molten state[204]. The use of non-isomorphous materials in eutectics is known to be accompanied by a mutual solubility threshold as the added compound can only fit into the lattice of the first agent to a certain extent. When the respective threshold of solubility is reached strain within the corresponding solid solution lattice causes

disorganization. A eutectic phase is then formed by generating an inter-phase boundary between two phases produced during reorganization. Redistribution of atoms occurs at the formed inter-phase boundary of solid solutions. The strain provided by non-isomorphous solids is further enhanced by defective anatomic rearrangement and weak bonding interactions at the inter-phase boundary. Therefore, this process lowers the melting point of eutectic systems due to the heightened thermodynamic functions[204].

For example, EMLA® a marketed eutectic system combining prilocaine and lidocaine as local anesthetics drastically improves transdermal permeability and aqueous solubility of the incorporated drugs, demonstrating the potential of these systems for permeation enhancement[207]. An article by Chu and Yalkowsky investigated the impact of melting point on drug absorption[179]. Their findings concluded that the absorption of drugs possessing a lower melting point is less influenced by the incorporated drug dose, revealing that reduced melting points can improve drug solubility and partitioning values[208]. Hence, eutectic systems can also be considered a potential alternative to supersaturated drug delivery systems. Supersaturated solutions significantly increase flux due to an enhanced driving force which renders permeation enhancement without the inclusion of permeation enhancers. However, supersaturated drug delivery systems are in a metastable thermodynamic state as precipitation of the supersaturated drug can occur[209]. Hence, by eliminating the risk of drug precipitation, eutectic systems can present a more stable alternative to supersaturated drug delivery systems.

In terms of the safety and potential toxicity of eutectic systems, there is a general perception that eutectics can be considered non-toxic mixtures as the parent molecules are regarded as green or safe to use. Pharmaceutical regulatory bodies therefore do not consider eutectic systems novel polymorphs and do not require new clinical trials to investigate their toxicity. However, safety concerns involving eutectic systems are being raised in the literature. Specifically, due to the lack of knowledge regarding the type of toxicity that may arise due to the instability observed during the formation of these systems. Moreover, research also revealed that high hygroscopicity of eutectic systems can lead to oxidation or chemical degradation of parent molecules[210,211].

3.4. *Combining liquid-based drug delivery approaches*

Combining liquid-based transmucosal drug delivery approaches has been reported as a strategy to enhance vehicle ability to cross mucosal barriers[212–215]. However, various physiological factors at specific mucosal sites often hinder mucosal barrier crossing, thereby creating obstacles to effective transmucosal drug delivery[73]. These challenges are summarized in Table 1[12,13,17,51,91,216-239] to compare the advantages to the reported challenges/disadvantages of site-specific transmucosal drug delivery.

Table 1 Advantages and challenges/disadvantages of ocular, nasal, oromucosal, and vaginal drug delivery.

Transmucosal route	Advantage	Challenge/disadvantage	Ref.
Ocular	Ease of administration	Blinking reflex	216,218
	Targeting of specific ocular sites	Drug binding to tear proteins	217,218
	Reduced risk of side effects	Drug dilution by tears	51,217
	Increased stability of drugs	Short contact time	217,219
	Reduced dosing intervals	Delivery to posterior sections requires crossing of numerous physiological barriers	217,220
	Improved mucosal retention	Avoiding systemic side-effects	217,221
		Cornea is a static barrier to drug diffusion	51
		Temporary vision impairment	91
Nasal	Viable option for systemic drug delivery	Rapid mucociliary clearance	222,225
	Direct nose-to-brain delivery by bypassing the blood −brain barrier	Potential enzymatic degradation	223
		Precisely targeting the drug to specific regions of the nasal cavity	223
	Localized drug delivery		222,226
	Bypassing hepatic metabolism	Potential for irritation or damage to the nasal mucosa with repeated use	223
	High epithelial permeability		222,225
	Swift onset of action	Low drug retention time	223,225
	Simplified administration	Often involves a drug/device combination	223,227
	Relatively low enzymatic activity		224
	Non-invasive vaccine administration site		223
Oromucosal	Direct delivery to the systemic circulation	Limited surface area	228,229,234
	Swift onset of action	Salivary washout	228,229,235
	Relatively low enzymatic activity	Potential for enzymatic degradation	228,229,234
	Suitable for patients with swallowing difficulties	Short residence time (swallowing)	230,236
	Excellent route for emergency treatments	Establishing sustained release	231,237
	Vaccination target site	Tongue movement	232,237
	Epithelial permeability	Eating and drinking can interfere with drug absorption	233,235
Vaginal	Large surface area for drug absorption	Permeability varies according to stage of menstrual cycle pH influenced by stage of menstrual cycle	13,238
	Bypassing liver metabolism		13,239
	Reduced occurrence of side-effects	Intercourse alters pH	77,238
	Dense network of blood vessels	Menstruation washes drug away	12,238
	Access to the uterine first-pass effect	Limited drug retention time	238,239
	Localized treatment during pregnancy	Leakage of formulations	12,238

To capitalize on the advantages listed in Table 1, combined liquid-based drug delivery approaches advance the capacity of established formulations to optimize their targeting potential and subsequent therapeutic efficacy. Examples include simple strategies such as mixing ionic liquids to impart improved physical characteristics to tailor conductivity, viscosity, and polarity as a means to improve drug solubility and mediate the crossing of mucosal barriers[73,240]. Advanced approaches are also reported such as the work of Lin and co-workers exploring the incorporation of oil-in-ionic liquid-based nanoemulsions intended for intranasal influenza split-virus vaccine delivery[215]. Their study involved mixing squalene (oil phase), Tween® 80 (surfactant), choline, and niacin (ionic liquid combination replacing traditional water phase) in a single-step ultrasonic method. The ionic liquid combination drastically improved emulsion stability compared to a conventional O/W counterpart emulsion. Moreover, their results revealed a 25-fold higher secretory IgA titers *via* adjuvant antigen induction compared to antigens that were not delivered *via* a combined liquid-based drug delivery approach. Additionally, the oil-in-ionic liquid-based nanoemulsion rendered a 5.8-fold superior antigen induction, systemic humoral, mucosal, and cellular immune response, compared to the commercially available MF59-adjuvant vaccination[215]. These favorable results were attributed to prolonged nasal mucosa retention mediated by the combined liquid-based drug delivery vehicle. This led to superior paracellular transport, expertly delivering antigens to the underlying submucosa. This success can also be attributed to the uniform nano-sized droplets mediating mucosal crossing of the incorporated antigens[215]. When considering the mucoadhesion theories, prolonged mucosal retention at the nasal mucosa could have been mediated by ionic liquid inclusion adhering to the mucus layer *via* electrostatic interactions to prolong mucosal retention time[73,241,242]. Moreover, ionic liquids can also improve wetting of the mucosal surface as promoted by the improved spreadability of the ionic liquid-nanoemulsion combination to optimize mucoadhesion[243,244]. The uniform, small droplet size of the nanoemulsion component can also promote diffusion through the mesh-resembling mucin network of nasal mucus[245]. Thus, demonstrating the genius of combining liquid-based drug delivery approaches to capitalize on multiple theories of mucoadhesion to render superior transmucosal drug delivery.

Combining liquid-based drug delivery systems can inspire innovative approaches that mimic viruses, which have naturally evolved to cross mucosal barriers through mechanisms of mucoadhesion and mucosal penetration[87,246,247]. By integrating these liquid-based formulations, it can be possible to create an effective platform that utilizes both mucoadhesion and mucosal penetration. However, before moving toward combined strategies, it is essential to have a comprehensive understanding of each liquid-based drug delivery system. Key considerations of the individual liquid-based drug delivery systems presented by this review are summarized in Table 2[21,73,75,138,142-144,152,170,171,174,175,181,196,207,248-286] to understand the targeting mechanism of these dosage forms when used individually or in combination to mediate the crossing of mucosal barriers guarding the ocular-, nasal-, oromucumosal-, and vaginal epithelia.

4. Liquid-based drug delivery approaches for ophthalmic administration

The eyes can be described as specialized organs permitting sensory awareness *via* impulse transmission processed into vision within the brain[287]. The eyes present a highly sophisticated physiology which can be divided into posterior and anterior segments[288]. The anterior segment occupies approximately one-third of the eye and includes the following ophthalmic structures: conjunctiva, cornea, aqueous humor, ciliary body, iris, and crystalline lens. The posterior segment refers to the remaining ocular structures (*i.e.*, sclera, Bruch's membrane, choroid, retinal pigment epithelium, vitreous humor and neutral retina)[289]. Pharmaceutical scientists are still challenged by ocular drug delivery due to various barriers provided by the complex ocular structures such as static barriers referring to the corneal stroma, stratified corneal epithelium, and sclera. Moreover, dynamic barriers like lymphatic clearance, conjunctival blood flow, and tear turnover rate combined with metabolic barriers such as enzymatic action and efflux pumps can impede ophthalmic drug delivery[290].

The main challenge for ophthalmic delivery systems is to reach an optimum drug concentration at the corneal surface to establish localized therapeutic efficacy[291]. Almost 95% of the ocular products on the market are developed for the topical route of administration[291,292]. The bioavailability of this route is as low as 5%, caused by various factors like tear/solution drainage, blinking, lacrimation, and tear dilution[291,292]. The cornea is the primary ocular transmucosal route for topical drug absorption[293]. The literature describes the cornea as a collagenous structure providing mechanical strength to the eyeball. The cornea presents a transparent nature to fulfil its light-focusing function on the retina[290]. The multilayered nature of the cornea is enforced by the presence of lipophilic and hydrophilic layers, which makes it relatively impermeable[293]. After crossing the tear film, the cornea presents five layers[294]. These layers are predominantly lipophilic, implying that the absorption of hydrophilic drugs can be difficult[293]. At a physiological pH the cornea presents acidic groups on the ocular surface and therefore negatively charged drugs may exhibit a slower absorption rate[293]. The barriers to ocular drug permeation are presented in Fig. 8.

Understandably, more than 95% of ocular products on the market are eye drops, with advantages like easy administration and efficient stability[295]. The majority of eye drops are aqueous based, with common negatives including rapid clearance combined with the failure to be retained at the corneal mucosa[176]. Simplicity of the products, ease of administration, convenience, good corneal penetration, patient compliance, lower toxicity and reduced side effects, are some of the advantages of ophthalmic drug administration[291,293]. Simplified administration is a necessity as geriatric patients are at higher risk of suffering from ocular conditions implying that formulators should avoid complex drug administration strategies to ensure patient adherence. Examples of ocular conditions include cataract formation, myopia, age-related macular degeneration, scarring, chronic dry eyes, diabetic neuropathy, post-operative endophthalmitis, proliferative vitreoretinopathy, inflammation, allergies, glaucoma, and fungal/bacterial keratitis[296].

Developing new drug delivery systems other than conventional ocular therapy to improve efficacy and bioavailability can present challenges[291]. Importantly, ideal ocular drug delivery vehicles should demonstrate good corneal penetration, prolong drug retention within the ocular mucosa, target specific areas of the eye to mediate a localized therapeutic effect, render sufficient bioavailability, and avoid vision impairment[296,297]. Most of the recent ophthalmic research attempts to increase the residence time of drug delivery systems[298]. The majority of research work is still in the experimental phases, and not commercially available yet. In

Table 2 Key considerations of transmucosal liquid-based drug delivery systems.

Drug delivery system	Key excipients	Targeting mechanisms	Outcomes	Ref
Nanoemulsions	Oil phase	Mucoadhesion	Increased bioactive stability of drugs	248,249
	Water phase	Reduced droplet size	Reported inability to cross corneal	248,250,252
	Surfactant/co-surfactant	Site-specific drug release	barrier	251
	Polymers		Superior brain targeting following	248,252
			intranasal administration	248
				253
SEDDSs	Oil phase	Mucoadhesion	Prolonged drug stability	144,143
	Water phase	Muco-penetration	Enhanced cellular uptake	75,144,254,256
	Surfactant/co-surfactant	Enzymatic encapsulation	Superior spreadability	144,255
		Enhanced drug solubility	Increased permeation	138,254
		Rapid emulsification in small fluid volumes		142
				152,254
Double-emulsions	Oil phase	Encapsulating hydrophilic and lipophilic drugs	Improved sustained release	21
	Water phase		Enhanced corneal permeability	21,258
	Surfactant	Enhanced drug solubility		21,257
	Co-surfactant			21,258
Sol-gel transition dosage forms	Thermo-responsive polymers	Increased spreadability	Superior reduction of intraocular pressure	171
		Mucoadhesion		170,260,261
	Water	Prolonged drug retention	Sustained release (intranasal)	170,259
		Reduced leakage	Enhanced nasal mucosa permeation	170,171,262
		Stimuli dependent site-specific drug release	Increased nasal retention time	170,260,262
			Sustained oromucosal release of multiple drugs	260
				263
			Increased mucosal wound healing due to shielding	264
Fluidgels	Biopolymers	Mucoadhesion	Superior vaginal mucosa coverage	174,175,265
	Water	Increased spreadability	Enhanced sprayability capacity	175,265
		Increased surface retention	(vaginal administration)	265
				265
Ionic liquids	Can fulfill role of: oil phase	Enhanced drug solubility	Effective nose-to-brain delivery	266
		Mucoadhesion	Good biocompatibility with oral	181,267,268
	water phase	Shielding mucin glycoproteins	mucosa	181,267,268
	Structural component	Altering viscosity and elasticity of mucus	Increased dissolution rate in synthetic saliva	73,181,269
		Prolongs contact time		73
			Superior mucoadhesion in saliva	73,270
				271
Liquid crystals	Surfactants	Superior drug loading	Prolonged drug bioavailability	196,272
	Polymers	Optimized drug release	(corneal application)	196,273
	Co-solvents	Mucoadhesion	Superior nose-to-brain and systemic	274,276,277,278
	Amphiphilic lipids		targeting (lipid molecules) following	275
			intranasal administration	279
			Prolonged oromucosal retention	280,281
			Enhanced oromucosal permeability	280,281
			Sustained release/prolonged retention (vaginal mucosa)	282
Eutectic systems	Fatty acids	Enhanced aqueous solubility	Controlled release (vaginal mucosa)	283,286
	Alcohols	Permeation enhancement		207,284,286
	Ionic liquids			285

this review, we will consider examples of experimental work to demonstrate the advances of liquid-based ophthalmic drug delivery systems.

4.1. Nanoemulsions

A recent study by Tran and co-workers incorporated cannabidiol into a nanoemulsion for ocular administration to relieve intraocular pressure and inflammation[252]. Cannabidiol is notorious for its chemical instability, extensive liver metabolization, and high lipophilicity impeding its clinical use. Hence, localized drug delivery in a suitable vehicle can potentially bypass first-pass metabolism and improve the stability of cannabidiol. The potential of cannabidiol micellular formulations described as nanoemulsions was tested on three human corneal cell lines used to construct an artificial human corneal substitute. Their findings concluded that nanoemulsions drastically improved the bioactive stability of cannabidiol. However, the produced nanoemulsions were not able to cross the corneal barrier[252].

4.2. Double-emulsions

The objective of another study involved the development of a cationic reverse micelle-based double-emulsion to improve the therapeutic activity of betaxolol hydrochloride in anti-glaucoma therapy[258]. The hydrophilic betaxolol hydrochloride was incorporated inside the core of reverse micelles in a W/O/W double-emulsion to generate sustained drug release while improving

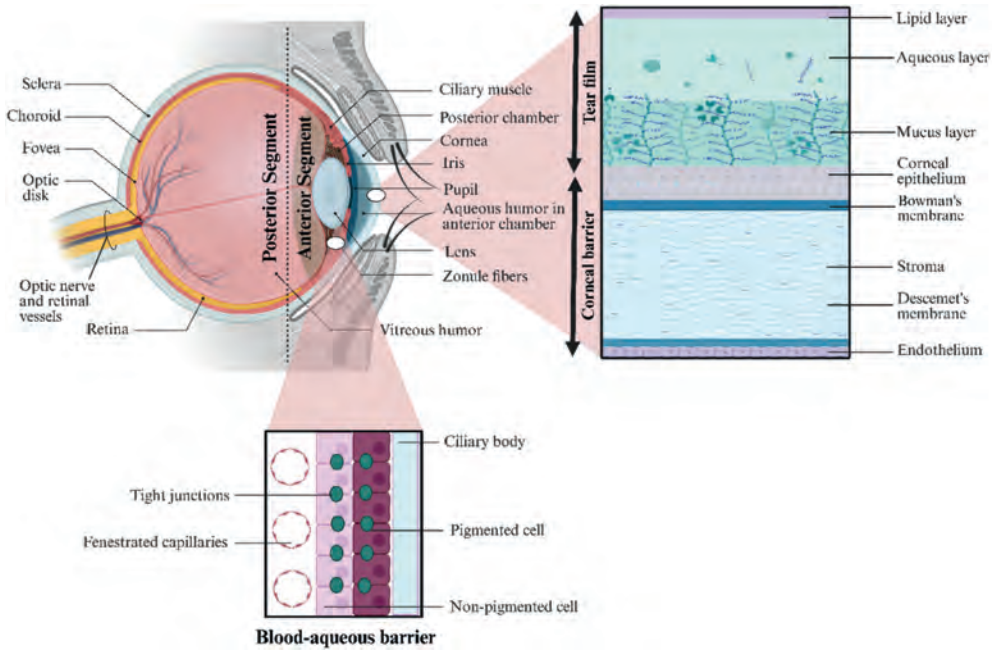

Figure 8 Barriers to ocular drug delivery[221]. Created with BioRender.

corneal permeability. A two-step emulsification process was used to produce the primary emulsion by homogenization followed by sonication to assemble reverse micelle formation. For reference, the method and excipients used to produce the aqueous and oil phases are thoroughly described by Sakr and co-workers[258]. The optimized W/O/W double-emulsion provided a sustained release for up to 7 h following the initial rapid release of betaxolol hydrochloride. Moreover, an *ex vivo* permeation evaluation revealed that the W/O/W double-emulsion rendered 2.5-fold enhanced permeation upon comparison to a marketed eye drop[252].

4.3. *Self-emulsifying drug delivery systems*

Generally, SEDDSs are employed to improve the aqueous solubility of lipophilic drugs[299]. Interestingly, a recent study proposed utilizing self-emulsifying oils for water-soluble drugs that do not remain stable in water for long periods of time such as the antibiotic cefuroxime sodium[256]. Cefuroxime sodium was suspended in self-emulsifying oils to guard against external water exposure during storage. Self-emulsifying oil phases comprised 5% *w/w* of either Cremophor® EL, Span® 80 and Tween® 20 combined with Miglyol oil. Benzalkonium chloride at a concentration of 0.01% *w/w* was also considered as an adjuvant cationic surfactant. Results of 6-month stability testing at a temperature of 40 °C revealed less than 2% chemical degradation of cefuroxime sodium in Span® 80 and Tween® 20 formulations. Moreover, the effect of benzalkonium chloride on chemical degradation was described as negligible. The suspended cefuroxime sodium transpired into spontaneous emulsions upon exposure to small fluid volumes. Thereby, signifying its potential as a substitute for conventional antibiotic eye drops[256].

4.4. *Liquid crystals*

A recent study suggested co-delivery of dorzolamide and timolol facilitated by liquid crystal nano cubosomes to mediate transcorneal drug delivery for glaucoma treatment[278]. At this point in time, the nanoscale co-delivery of dorzolamide and timolol is a novel scientific contribution, as the literature only reports individual nanoencapsulation of these drugs. Glycerol monooleate and poloxamer 407, together with the two drugs, were stirred, homogenized, and probed to produce liquid crystals. The cubosomes presented an average size of 143.5 ± 2.3 nm, zeta potential of 26.3 ± 1.7 mV, and PDI of 0.164 ± 0.014. Dorzolamide and timolol were encapsulated at a concentration of 84.5 ± 2.1% and 91.3 ± 2.7%, respectively. Importantly, *in vitro* evaluation revealed gradual release for both drugs providing a maximum dose 24 h after administration. Moreover, *in vivo* studies performed on New Zealand rabbits revealed reduced intraocular pressure 4 h after liquid crystal administration. Pharmacokinetic experiments depicted prolonged bioavailability compared to a commercial product. Additionally, histopathological studies identified the nano cubosome liquid crystals as optimally biocompatible with corneal epithelia[278].

4.5. *Phase transforming liquid formulations*

In terms of stimuli-responsive drug delivery systems, temperature is most often used as a trigger for phase transition regarding ocular drug delivery[300]. For instance, a study attempted to minimize intraocular pressure by developing thermo-responsive gels incorporating the prodrug dipivefrin hydrochloride containing poloxamers (P407 and P188)-carbopol-934. These polymer-based gels provided simplified application due to their solution-like nature. External stimuli can transform these solutions to form a gel, which prolongs the ocular residence time due to improved viscosity and mucoadhesive properties[301,302]. External stimuli included temperature, pH and the presence of ions[301]. A thermo-responsive gel transforms through the sol-gel phases after temperature changes[261]. This system shows a superior ability to reduce elevated intraocular pressure in rabbit eyes[261].

Ion-activated polymers like gellan gum and alginic acid are also used in ophthalmology formulations[303]. To prolong ocular

residence time, alginic acid, a biodegradable and biocompatible polysaccharide, is successfully used[304,305]. This polysaccharide is useful since it increases the ocular drug resistance time due to its mucoadhesive and gel formation properties[304]. This can be attributed to the double helices formation *via* weak van der Waals forces produced by gellan gum at room temperature. The lacrimal fluid consists of cationic electrolytes, and upon contact between gelling agents and lacrimal fluid, these helices aggregate leading to crosslinking of the polymer. This resulted in formed complexes with the cations and hydrogen bonds of the water to improve ocular residence time[306–308].

4.6. *Eutectic systems*

A recent review article written by Sarmento and co-workers raises the question of whether deep eutectic systems obtained from a natural origin can enhance the efficacy of ocular therapeutics[309]. This excellent review considers the different layers of the cornea that must be permeated during transmucosal drug delivery and how deep natural eutectic systems can modify viscosity, be a bioactive excipient, improve aqueous solubility, and provide superior stabilization of drug delivery systems to enhance ocular drug delivery[309]. As an example, this study referred to a study performed by Achkar and co-workers that developed novel supramolecular deep eutectic systems *via* levullinic acid and cyclodextrin inclusion[310]. These unique systems provide multiple drug encapsulation due to the presence of cyclodextrin while improving the permeation of mucosal barriers[310]. Thereby, signifying that natural eutectic systems might be the next hot topic in ocular drug delivery.

5. Liquid-based drug delivery approaches for nasal administration

The main function of the nose is to filter out airborne particles, to heat and humidify inhaled air and to provide a mechanism for olfaction. Although the well-perfused mucosal epithelial surfaces of the nasal cavity are designed to protect the body against the uptake of unwanted foreign materials, they also provide an opportunity for drug absorption after nasal administration[311].

Evidence exists that people have administered traditional medicines into the nose since ancient times, but the use of nasal sprays for modern medicines commenced approximately in the middle of the 20th century. These original nasal spray products were mainly intended for local action in the nose (*e.g.* for the relief of nasal congestion experienced during diseases such as allergic rhinitis). However, nasal drug delivery products have since evolved tremendously and the nasal route of drug administration has become a useful alternative for the administration of drugs for systemic delivery[312,313]. Furthermore, it was discovered that the nasal route of drug administration not only provides a viable option for systemic drug delivery, but it also provides an opportunity for delivery of drug molecules into the brain[314].

Direct nose-to-brain drug delivery after nasal administration provides an effective, advantageous and non-invasive way to treat neurological and mental diseases of the central nervous system due to avoidance of the blood–brain barrier. By deposition of the drug dose in the olfactory region of the nasal cavity during administration, the nasal route of drug administration can specifically be used to target drug delivery to the brain[315]. Delivery of drug molecules into the brain after nasal administration can occur through different pathways of absorption (as presented in Fig. 9).

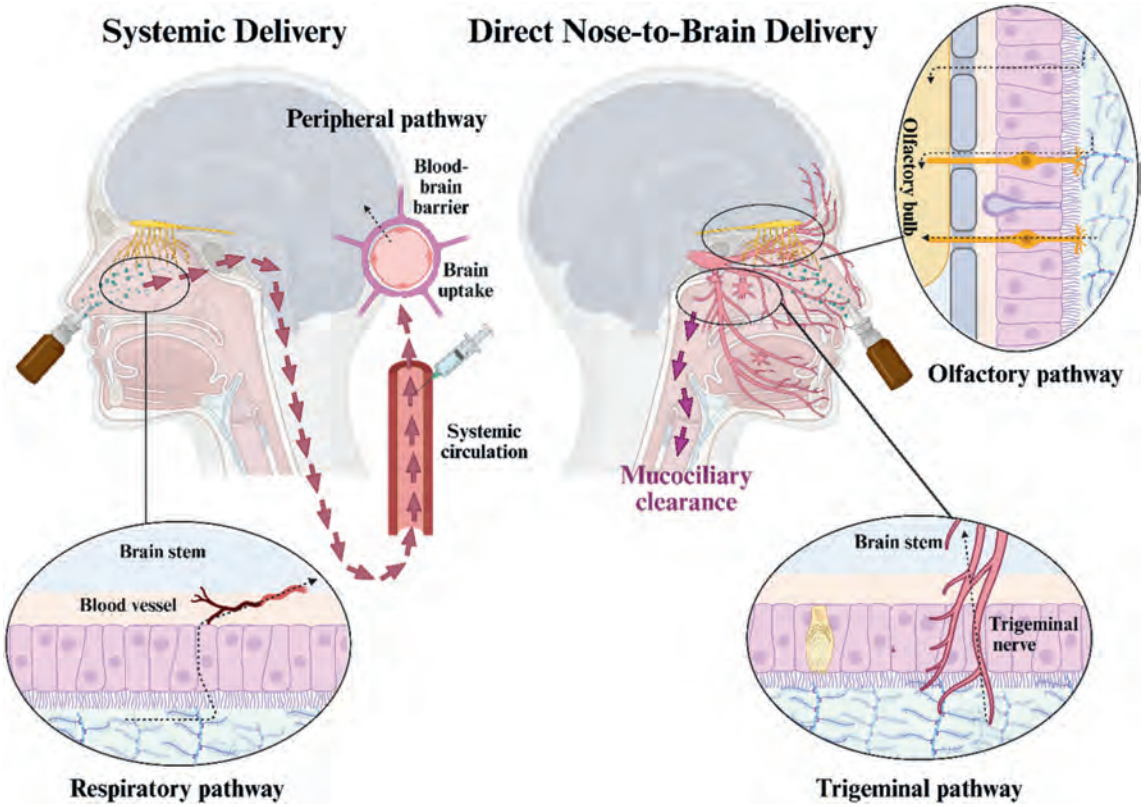

Figure 9 Schematic representation of pathways for intranasal drug delivery[316,317]. Created with BioRender.

Namely by diffusion across the olfactory epithelium or through uptake *via* the olfactory neurons (olfactory pathway) and/or through uptake *via* the trigeminal nerve (trigeminal pathway). In addition, drug molecules can be indirectly delivered into the brain after nasal administration (respiratory pathway) *via* the systemic circulation, but then the drug molecules need to cross the blood−brain barrier (peripheral pathway)[223].

The nasal route of drug administration is specifically suitable as an alternative to the oral route of drug administration for delivery of drugs that are active in relatively small doses and that are highly susceptible to first-pass metabolism[318]. The nasal route of drug administration is also useful for targeted delivery of drugs for the treatment of central nervous system diseases, where drug levels in the brain are usually hampered by the blood−brain barrier when these drugs are administered by the oral and parenteral routes of drug administration[315]. Unfortunately, the nasal route of drug administration is less suitable for treatment of chronic conditions that require multiple daily doses over an extended period of time and also conditions that are treated with drugs that require relatively large doses due to the limited volume and surface area available in the nasal cavity[319,320].

The application of the nasal route of drug administration will be demonstrated here by giving examples of drug products currently available on the market for treatment of various conditions. Firstly, nasal medicinal products are available for local action in the nose to treat diseases affecting the nasal cavity such as allergic and non-allergic rhinitis (*e.g.*, antihistamines and steroidal anti-inflammatory agents), nasal congestion (*e.g.*, vasoconstrictors), intranasal anesthesia (*e.g.*, local anesthetics) and nasal polyps (*e.g.*, corticosteroids). A wide variety of nasal drug products are available for nasal administration to afford a systemic action to treat diseases or conditions such as general pain (*e.g.*, opioid analgesics), diabetes insipidus (*e.g.*, hormones such as desmopressin), post-menopausal osteoporosis (*e.g.*, hormones such as calcitonin) and for smoking cessation (*e.g.*, autonomic ganglia stimulants). Nasal products are available for the treatment of neurological and mental diseases such as migraine (*e.g.*, ergot alkaloids and selective serotonin agonists), epilepsy related seizures (*e.g.*, benzodiazepines) and resistant major depression (*e.g.*, *N*-methyl-D-aspartate receptor antagonists)[312,321,322]. Lastly, the nasal route of drug administration is also highly suitable for the administration of emergency or rescue therapeutics due to its rapid onset of pharmacological action and ease of administration. In this regard, nasal products are currently commercially available for the treatment of opioid overdose (*e.g.*, opiate antagonist such as naloxone) and treatment of seizures during epilepsy attack (*e.g.*, benzodiazepines such as midazolam)[312,321].

5.1. Ionic liquids

Ionic liquids can be formed through ionic interactions between anions and cations, which have been explored as functional excipients in formulations to improve drug delivery *via* different routes of administration. Choline-based ionic liquids have initially been explored as permeation enhancers for the transdermal delivery of both macromolecules and small molecules with poor water solubility[323,324], but later also for enhanced drug delivery *via* the nasal route of drug administration. The ability of ionic liquids to enhance the adhesion and residence time of molecules on nasal mucosal surfaces has specifically stimulated research into using this formulation technique for improving drug delivery into the systemic circulation or into the brain after nasal administration[325].

Choline-based ionic liquid formulations have been investigated using both *in vitro* and *in vivo* models for the enhancement of nasal glucagon delivery. In this study, choline geranic acid and choline citric acid have been used to form ionic liquids for enhancing the permeation and prolonging the retention time of glucagon after intranasal administration. Intranasal delivery of glucagon in the form of ionic liquids elicited a rapid reversal of acute hypoglycemia in type 1 diabetic rats without leading to rebound hyperglycemia. In addition, electrostatic interaction was identified as the mechanism by which ionic liquids improve the transcellular transport of glucagon across the Calu-3 cell monolayer model, which serves as an *in vitro* model for nasal epithelial surfaces. The ionic liquids could also transiently open intercellular tight junctions to facilitate the paracellular transport of glucagon. Although continuous intranasal administration of ionic liquids led to changes such as inflammation in the epithelial cells, goblet cell overgrowth and distribution changes of the cilia, they were reversible and the nasal epithelium was able to repair itself[325].

A study that investigated the effect of an ionic liquid formulation on the nose-to-brain delivery of etodolac in mice after nasal intranasal administration showed high potential of these formulations for improved drug delivery to the central nervous system. The results exhibited an approximate 7-fold increase in etodolac delivery into the brain when compared to that of etodolac solution alone. Furthermore, the solubility of etodolac was improved approximately 200-fold by ionic liquid formation in simulated nasal fluids. The increase in the nose-to-brain delivery of etodolac was also partially attributed to the enhanced retention of the compound on the nasal mucosal surface due to the higher viscosity of the ionic liquid as compared to that of the solution[268].

5.2. Liquid crystals

Liquid crystal formulations have been investigated as a novel approach for enhanced systemic and brain delivery of drugs after nasal administration. One example of such a study is where liquid crystal formulations were prepared with monoglycerol ester and glyceryl monooleate for tranilast delivery into the systemic circulation as well as into the brain after intranasal administration in Sprague Dawley rats. The monoglycerol ester liquid crystal formulation exhibited a 10-fold increase in tranilast exposure in the whole brain ($AUC_{0-8} = 94.5 \pm 3.68$ ng h/mL) as compared to the solution formulation (control group, $AUC_{0-8} = 9.55 \pm 2.17$ ng h/mL). Furthermore, when ethanol and a non-ionic surfactant (Pluronic® F-127) were included in the liquid crystal formulation, the tranilast exposure in the whole brain ($AUC_{0-8} = 114 \pm 5.92$ ng h/mL) increased by 12-fold. Furthermore, the monoglycerol ester liquid crystal formulation containing ethanol and Pluronic® F-127 caused a 3.8-fold increase in tranilast blood plasma level ($AUC_{0-8} = 725 \pm 33.1$ ng h/mL) as compared to that of the solution formulation ($AUC_{0-8} = 189 \pm 16.2$ ng h/mL). The results from this study therefore showed that liquid crystal formulations prepared from monoglycerol ester have particular high potential for enhanced delivery of lipid drug molecules into the brain and systemic circulation after nasal administration [279].

5.3. Nanoemulsions

Different nanocarrier type dosage forms have been investigated to improve drug delivery to the brain after nasal administration, which include lipid-based nanoparticles, polymeric-based

nanoparticles, polymeric micelles, nanosuspensions, nano-vesicular spanlastics, dendrimer-based nanoparticles, nano-sponges, neosomes and nanoemulsions[326]. The use of nano-emulsions to target brain delivery after nasal administration has been reviewed elsewhere[253,327]. In general, it was found in several studies that nanoemulsions provide a non-toxic formulation strategy to improve nose-to-brain delivery of neurotherapeutic drugs. To demonstrate the efficacy of nano-emulsions in enhanced nose-to-brain drug delivery, some examples of nanoemulsion formulations used for investigations on drug delivery into the brain and efficacy after nasal administration will be described here.

Mucoadhesive nano-based drug delivery systems can be prepared by using chitosan as a coating material, which has proven effective in enhancing the delivery of therapeutic agents to the central nervous system after nasal administration. The *ex vivo* permeation and *in vivo* brain delivery of luteolin in Wistar rats when formulated in chitosan-coated nano-emulsion showed 6-fold and 4.4-fold increases, respectively, when compared to that of free luteolin. The improved delivery of luteolin when formulated in the nano-emulsion was attributed to the mucoadhesive properties of the chitosan-coated nanoemulsion formulation, which could improve the time of contact of the luteolin to the nasal epithelium, and the very small diameter of the nanoemulsion droplets[134]. In another study, a chitosan-coated nano-emulsion was developed for the chemotherapeutic agent, temozolomide, to improve its nose-to-brain delivery for treatment of glioblastoma multiforme. This chitosan-coated nanoemulsion significantly enhanced the *ex vivo* mucosal permeation of temozolomide when compared to the free drug and the nanoemulsion drug delivery system has also exhibited enhanced *in vitro* uptake of temozolomide into brain cells[328]. Sildenafil formulated in a chitosan-coated nanoemulsion showed increased efficacy (as determined by oxidative stress markers) in a hyperlipidemic rat model as compared to a sildenafil suspension formulation[329].

When docosahexaenoic acid concentrations are decreased in the brain, it increases the risk for development of Alzheimer's disease. It has been suggested that supplementation of the brain with docosahexaenoic acid may contribute to prevention of Alzheimer's disease. A nanoemulsion formulation containing docosahexaenoic acid did not show any detrimental signs in the viability of RPMI 2650 cells as measured with MTS assays. Intranasal administration of a nanoemulsion of docosahexaenoic acid in Hemizygous hAPPSwInd transgenic (J20) mice had positive effects on the cognitive behavior of the mice through counteracting oxidative stress, neuroinflammation and amyloid plaque formation[330].

5.4. *Phase transforming liquid formulations*

A thermosensitive gel can be defined as a specialized type of hydrogel that transforms from a solution to a semi-solid gel in response to environmental stimuli such as temperature, pH or ionic strength. In this regard, the thermosensitive gel exists in the free-flowing liquid state at ambient temperature, but turns into a highly viscous gel at physiological temperatures (*e.g.,* 32−37 °C) by means of sol-gel transition. Although liquid-based dosage forms such as metered dose nasal sprays are the most commonly used formulations for intranasal drug administration, they exhibit short retention times in the nose due to removal by mucociliary clearance. The use of thermosensitive gels showed special application for increased nose-to-brain drug delivery after intranasal administration due to increased residence time in the nose as compared to that of solutions[331]. Several studies have investigated novel strategies to further improve the physical properties of thermosensitive gels for more efficient drug delivery after nasal administration. These strategies included the incorporation of functional excipients or nanocarriers into the thermosensitive gel formulations. One such study investigated the incorporation of graphene-oxide in a thermosensitive chitosan hydrogel for intranasal delivery of rasagiline mesylate. In this work, the incorporation of graphene-oxide showed a significant concentration-dependent effect on the physical and mechanical properties of the thermosensitive chitosan hydrogel such as a decrease in the gelation time, porosity, and swelling of the hydrogel, but an increase in gel strength[332]. In another study, the mixing of different poloxamer polymers in several ratios as well as incorporation of hydroxypropylmethylcellulose showed improved mucoadhesion properties. The optimized thermosensitive hydrogel showed high potential for carbamazepine delivery to the brain after nasal administration[260]. Moreover, nifedipine was formulated into a nanostructured lipid carrier-based intranasal *in situ* gelling system, which showed optimal gelation time, temperature, and pseudo-thixotropic behavior, sustained release and enhanced permeation across the nasal mucosa. Furthermore, *in vivo* administration of the thermosensitive gel containing nifedipine in lipid nanocarriers revealed substantial improvement in cognitive ability along with reduced oxidative damage in an Alzheimer's disease Wistar rat model[262].

6. Liquid-based drug delivery approaches for oromucosal administration

The oromucosal, or pre-gastric, route of drug administration consists of the buccal (between the gums and cheeks) and sublingual (under the tongue) routes and has shown great promise in recent decades as an alternative route of drug administration[228]. Several physiological factors make the mucosal membranes of this route highly permeable, such as its low degrees of epithelial thickness and keratinization.

Concretely, the thinnest regions of the oral cavity can be found in the floor of the mouth, inner sides of the cheeks and lips, and ventral side of the tongue, *i.e.*, the very regions which constitute the buccal and sublingual routes of administration. These oromucosal regions are indicated in Fig. 10. A major reason being that these regions consist of non-keratinized stratified squamous epithelium[228,333]. The pH of the buccal mucosa is also more neutral, with a reported average value of 6.28 ± 0.36[70], making it more amicable to drugs that might degrade or denaturate in lower pH environments. Moreover, the intercellular spaces of the epithelium in the upper third of the inner sides of the cheeks are tight junction-free. Instead, these spaces are filled with lipids, facilitating the rapid permeation of small lipophilic molecules[334,335].

Apart from the physiological advantages of the oromucosal route, there are also several patient or treatment related problems that can be addressed by administering drugs *via* this route. These include sub-therapeutic drug concentrations, and irregular or inappropriate drug use, potentially leading to treatment discontinuation[338−341]. The above-mentioned negative therapeutic outcomes are more prevalent geriatric and pediatric patients, as well as dysphagic patients, highlighting the growing need for patient-centered pharmaceutical development[231,340,342]. The oromucosal route, with its high permeability, rapid onset of action,

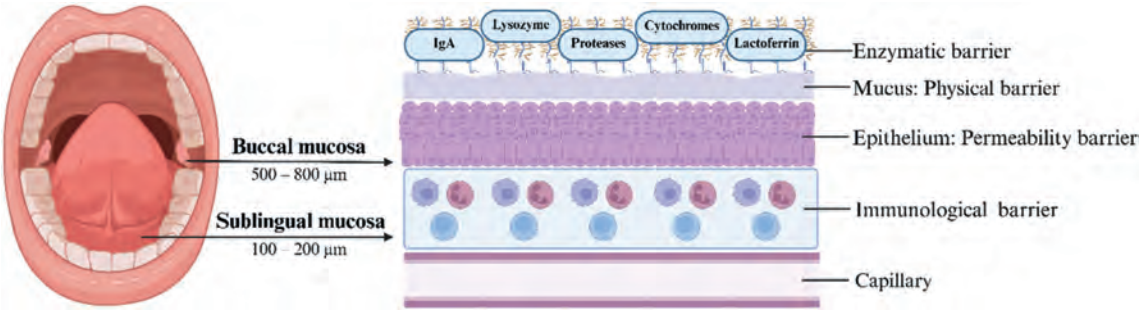

Figure 10 Mucosal barriers to oromucosal drug delivery[247,336,337]. Created with BioRender.

and no need to swallow (for patients with dysphagia), might be an appealing route of drug administration for future pharmaceutical development.

An excellent review by Bastos and co-workers[231], explored the oromucosal products currently on the market, highlighting the broad range of conditions that are currently treated using this route of administration. Examples of these conditions include allergic rhinitis and asthma, chronic pain, opioid dependence, angina, recurrent herpes labialis, and allergic conjunctivitis. The dosage forms of these products mostly include sublingual tablets, wafers, powders, drops, and sprays, as well as buccal films and mucoadhesive buccal tablets[231]. In this paper, we will explore recent examples of liquid-based formulations for oromucosal drug delivery.

6.1. *Ionic liquids*

Several studies have suggested that ionic liquids may offer an exciting means of delivering drugs *via* the oromucosal route. Vaidya and Mitragotri (2020) developed mucoadhesive buccal patches of insulin-containing choline and geranic acid (CAGE)-polyvinylalcohol-based ionic liquids and assessed the systemic delivery thereof in rats[269]. Not only were the insulin/CAGE ionic liquids able to give a dose-dependent reduction in blood glucose levels of up to 50%, but the patches also did not cause significant damage to the epithelial tissue, suggesting good biocompatibility[73,269].

Ng and Hadinoto (2024) developed gelatin films loaded with imidazolium-based ibuprofen salt ionic liquids, and assessed the effects of ionic liquid loading on the films' mechanical strength, inter-batch dosage uniformity, thermal stability, and dissolution and solubility enhancement[270]. Their results showed good inter-batch drug content uniformity, with an acceptance value (AV) of 15%. The dissolution rate of ibuprofen in simulated saliva fluid was also sufficiently enhanced, to 100% in 15 min[270].

Although not a drug delivery study, Medeiros's group[271] developed mucoadhesive films containing chitosan and protic ionic liquids, to act as wound dressings on the oral mucosa. Their results suggested that films based on chitosan and containing 35% to 50% (*w*/*w*) 2-hydroxy diethylammonium protic ionic liquids had superior mucoadhesive properties, antimicrobial activity, and flexibility in synthetic saliva.

6.2. *Self-emulsifying drug delivery systems*

Another formulation strategy that has found novel application in the oromucosal route of drug administration, is that of SEDDSs. Since SEDDSs are known to improve the cellular uptake of entrapped drugs[76,343], it might be an appealing approach to enhance the permeation of drugs with limited mucosal tissue penetration.

Friedl's group[143], investigated SEDDSs as a possible enhancer of the buccal delivery of curcumin, a biopharmaceutics classification system (BCS) class IV drug. Their delivery system was a mucoadhesive patch, consisting of two intersecting fiber types. The first type of fiber consisted of thiolated polyacrylic acid, while the second type consisted of a water-insoluble polymer containing curcumin-loaded SEDDS. As saliva passes through the patch, the second fiber type releases the SEDDS as nanoemulsions. As a control, the same mucoadhesive patch was developed, but containing only curcumin (not SEDDS) in the second fiber type. The patches were then applied to excised porcine buccal tissue and studied. The results suggested that the patches containing SEDDSs were able to dramatically enhance the penetration of curcumin into buccal tissue, relative to the SEDDS-free patches. These findings suggest that SEDDS formulations can be a viable drug delivery approach for the oromucosal administration route.

6.3. *Liquid crystals*

The use of a methylene blue-loaded mucoadhesive liquid crystal precursor system (LCPS), intended for the treatment of oral cancers *via* the buccal route of administration, was investigated by Balian and co-workers[344]. Their rationale for using LCPSs was based on the knowledge that these systems can give sustained drug release at the site of administration[345,346], and turn into gels upon contact with saliva, increasing the residence time in the oral cavity[280,281]. Furthermore, their LCPS contained polyethyleneimines and chitosan as mucoadhesive polymers, further adding to the residence time of the LCPS in the oral cavity, thereby possibly enhancing the efficacy of the treatment[276,277]. Indeed, their results showed that methylene blue in their LCPS was retained twice as long as its permeability, suggesting that adequate maintenance of therapy in the oral cavity could be achieved. The methylene blue-loaded LCPS also showed an increase in antitumor activity, compared to the control[344].

6.4. *Phase transforming liquid formulations*

Bender's group[263] developed a phase-transitioning sol-gel system based on Carbopol 934P NF and Pluronic F-127 blends, containing lidocaine and metronidazole. The rationale behind their formulation was to have the sol-phase make contact with the inner surfaces of the empty tooth socket, followed by a transition to the gel-phase. The resulting monolithic gel-phase then remains in the socket, preventing the ingress of debris and providing sustained release of lidocaine and metronidazole at sub-toxic levels, thereby

providing pain relief and protection from bacterial growth. Their results showed that at 23.38% Pluronic F-127, the gelation of their sol-gel started at 23 °C, and was complete at 37 °C. The gel-phase was able to give sustained release of both drugs over 24 h, at therapeutically relevant concentrations. Although not strictly oromucosal delivery, the findings presented by Bender and co-workers suggested that phase-transforming sol-gels can be used to treat wounds in the oral cavity, and can therefore possibly find future uses as oromucosal administration devices[263].

Phase transforming liquid formulations were explored recently by Zhang and co-workers, who developed an oil that transitions to a gel, *in situ*, to treat oral mucositis[264]. Oral mucositis is a common complication of cancer therapy, occurring in up to 80% of patients receiving high-dose radiotherapy[347]. It is also a serious complication, possibly resulting in anorexia and significant weight loss due to dysphagia, dehydration, and dysgeusia, brought about by the severe pain experienced by patients suffering from oral mucositis[348]. The rationale behind the development of their *in situ* gel-forming oil was to provide treatment in the form of physical shielding, while α-lipoic acid (solubilized in the oil) is slowly released from the resulting gel, acting a natural antioxidant. Their results showed that, after coming into contact with saliva, their oil was able to rapidly transition into a gel, thereby adhering to the oral mucosa. Their oil also showed excellent adhesion energies of 3.9 ± 0.2 N and 60 ± 2 J/m^2, on excised porcine buccal tissue. In their oral mucositis mouse model, application of their oil showed improved mucosal wound healing, inhibition of pro-inflammatory cytokines, and new granulation around the wounds[264]. The results therefore suggest that an *in situ* gel-forming oil, acting as a carrier for lipophilic drugs, can be an exciting approach in the treatment of oral mucositis, and possible other wounds in the oral cavity.

7. Liquid-based drug delivery approaches for vaginal administration

The first written records of vaginal drug administration practices date back to ancient Egypt, specifically circa 1850 BCE, where the vaginal route is considered one of five main drug administration routes[349,350]. Vaginal drug administration is an increasingly promising route for drug delivery despite its dynamic physiological environment (as displayed by Fig. 11), particularly for drugs with unfavorable physicochemical properties, such as poor aqueous solubility, which negatively affects oral bioavailability[239,351].

Vaginal drug absorption into the peripheral circulation is mediated by a venous plexus directing drugs to the hemorrhoidal- and internal iliac veins[351,355,356]. Hence, vaginal drug administration can bypass first-pass hepatic metabolism, thereby enabling the use of lower drug doses while improving therapeutic efficacy[351,355,356]. Importantly, localized drug delivery to the uterus can be facilitated by vaginal administration due to what is known as the uterine first-pass effect[12,83,354,357]. This phenomenon facilitates targeted drug delivery to the uterus *via* a counter-current drug exchange between the arterial and venous networks involved in both vaginal and endometrial perfusion[83]. The literature describes the uterine first-pass effect as an underutilized mechanism in the realm of female reproductive health[354]. By leveraging the uterine first-pass effect, various diseases of the upper female genital tract can be effectively treated, minimizing the side effects associated with systemic absorption[12,83,354,357]. This approach could also allow for targeted treatment during pregnancy by managing conditions like premature birth[358].

Egyptian gynecological records reveal that the vaginal route of administration was reserved for practices such as abortion, pregnancy prevention, and treatment of pregnancy-related health conditions implying that the Egyptians delivered therapeutics *via* the uterine first-pass effect[349,350]. Generally, modern-day vaginal formulations are designed to elicit local effects such as antimicrobial, antifungal, or spermicide activity[359]. Additionally, there is a growing interest in using vaginal drug delivery systems for microbicides to prevent sexually transmitted infections, including those caused by the human immunodeficiency virus, human papillomavirus, and herpes simplex virus[359]. When developing liquid-based formulations for vaginal administration, it is crucial to consider how excipients might affect the physiological balance of the vaginal microbiome as the acidic pH of the vaginal environment is maintained by lactic acid-producing bacteria

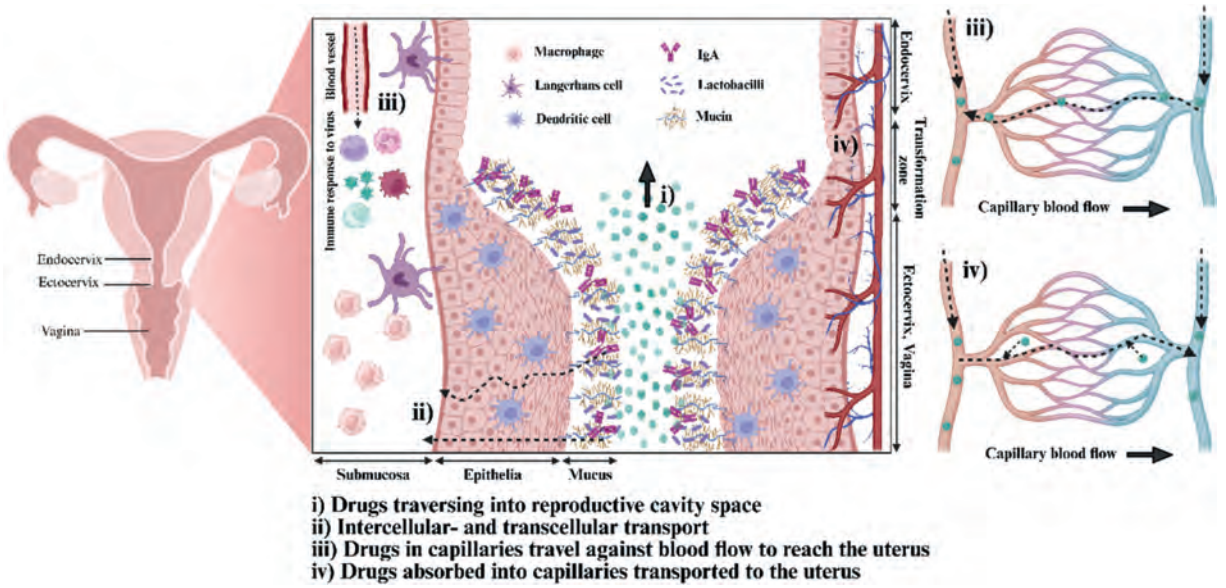

Figure 11 Mechanisms of the uterine first-pass effect following vaginal drug administration[352–354]. Created with BioRender.

species[360]. Therefore, disrupting the natural protective microbiota can lead to infections while attempting to treat another condition. Furthermore, maximizing drug efficacy requires delivery strategies that minimize leakage, reduce user discomfort, limit local irritation, and take into account physiological changes, such as menopause or sexual intercourse, that can affect vaginal pH, subsequently impacting drug delivery[238,361−363].

Significant advancements have been made in the development of liquid-based formulations aimed at improving drug retention in vaginal mucosa[118,238,346,359,364]. Retention within the vaginal epithelium can be facilitated by controlled release from liquid-based dosage forms to reduce dosing intervals while optimizing localized therapeutic efficacy. Typically, traditional semi-solid dosage forms fall short due to leakage necessitating frequent dosing[238]. This is especially concerning when treating localized fungal and bacterial infections as antimicrobial resistance can develop ultimately requiring systemic treatment alternatives[365].

7.1. Emulsions

A study by Campaña-Seoane and co-workers incorporated ciprofloxacin in mucoadhesive water in silicone emulsions to study its absorption, distribution, and vaginal residence time in an *in vivo* rat model preceded by *in vitro* release experiments[366]. *In vitro* drug release profiles demonstrated zero-order kinetics with constant ciprofloxacin concentrations being released over a minimum period of 6 h. The *in vivo* data revealed significant distribution to the uterus and ovaries within 24 h of intravaginal administration. Water in silicone emulsions contains no oil phase but instead harbors water or aqueous saline solutions within a non-polar external phase comprising low molecular weight silicone-based polymers[366]. Silicone promotes tissue adhesion to withstand clearance by vaginal fluid in a dynamic physiological environment. Compared to hydrogels water in silicone emulsions provides an attractive mucoadhesive alternative since hydrogels swell following adhesion to mediate drug permeation. However, the swelling mechanism can give rise to structural deformity of the dosage form and reduced bioadhesion.

7.2. Phase transforming liquid formulations

As an additional alternative to hydrogels, the literature reports the incorporation of doxycycline in a mucoadhesive, thermos-responsive sol-gel to avoid sexually transmitted infections. The sol-gels were optimized *via* preparation in a buffered medium mimicking vaginal pH and osmolarity. The authors reported that mucoadhesion was unaffected by vaginal fluid secretions and that gelling was maintained at body temperature to ensure protection against vaginal infections by sustaining minimum inhibitory concentrations of doxycycline[171].

Thermo-responsive gels present the opportunity for vaginal drug administration as a liquid can be inserted, but leakage is avoided due to transition to a gel after administration. Gel transitions can be mediated by including thermosensitive polymers above their critical gel concentration. Interestingly, a study by Shapiro and co-workers reported utilizing a hypotonic liquid combined with a thermosensitive polymer below its critical gelling concentration to improve the initial spreadability of a uniform and thin fluid layer[367]. As the polymer was included below the critical gelling concentration, gel formation only occurred upon water absorption as procured from the vaginal mucosa to restore the osmotic equilibrium. This study also reported reduced cytotoxicity compared to a gel formulation and that the fluid formulations were compatible with the vaginal microbiota[367]. Spray gels have also emerged as adaptable vaginal dosage forms as thermosensitive polymer combinations can be used to capitalize on the pH influence of the vaginal environment by considering the inclusion of a pH-responsive polymer like chitosan while combining it with other thermos-responsive polymers to mediate mucoadhesion such as hydroxyprophylmethylcellulose[265]. Additionally, spray gels hold the advantages of covering a larger surface area in a short time frame. A recent study revealed that a spray gel released the highest cumulative percentage of miconazole nitrate (*i.e.*, 81.72%) compared to a commercially available cream and suspension exhibiting a release percentage of 57.63% and 34.03%, respectively[265].

In contrast to fluids transpiring into stimuli-responsive gels, vehicles like fluid gels are known to exhibit reduced viscosity upon shear application which can simplify handling due to their semi-solid nature while reversing to a fluid consistency upon vaginal application. These formulations retain their semi-solid form after the force of application has been removed to avoid leakage. Recently, Robinson and co-workers developed a fluid gel from alginate gelation while including acetic acid as an antimicrobial as well as a gelling agent[368]. These fluid gels demonstrated increased surface coverage due to their improved sprayability rendered by a discretized microstructure characterized by elevated elasticity and increased viscosity. Despite increased viscosity, the fluid gels were easily sprayed due to shear application causing fluid formation. This study investigated acetic acid fluid gels for the treatment of burn wounds[368]. However, acetic acid has been utilized to locally treat infections of the vagina and ears[368]. Signifying that this study can provide a foundation for future acetic acid fluid gels destined for vaginal administration, especially in low-resource environments.

7.3. Nanoemulsions

Natural active ingredients such as essential oils have also garnered scientific attention in transvaginal drug delivery due to their favorable antifungal and antibacterial properties[369]. Essential oils are interesting alternatives to laboratory-synthesized drugs as the literature fails to report antimicrobial resistance to these compounds due to their bioactive composition[370]. However, essential oils present stability challenges when exposed to heat, oxygen, humidity and light[369]. Moreover, these are volatile substances requiring a lipophilic vehicle to compensate for their poor aqueous solubility[369]. Interestingly, Gündel and co-workers investigated nanoemulsions as a lipophilic carrier to improve the instability of eucalyptus/lemongrass essential oils for treatment of vulvovaginal candidiasis[369]. An *in vivo* murine model demonstrated that the free form of considered essential oils exhibited no antifungal activity and the nanoemuslions harboring essential oils demonstrated superior antifungal activity compared to the miconazole treatment of the control group[369].

Apart from utilizing nanoemulsions as a vehicle for natural ingredients, nanoemulsions also allow incorporation of natural ingredients to enhance the therapeutic action of laboratory-synthesized drugs. As an example, Ho and co-workers developed a squalene-based nanoemulsion as an adjuvant to a model immunogen vaccination in mice[371]. This is an emerging field of research to induce mucosal immunity in the lower genital tract after local antigen administration to create immunity against genital infections. The squalene-based nanoemulsion increased

retention time in the vaginal mucosa while facilitating humoral and cellular immunity on an antigen-specific basis[371]. Emulsions can be described as a very versatile vehicle due to their tailorability by including different stabilizing agents. Generally, surfactants are included for this purpose. However, a recent publication by Zhao and co-workers reported the innovation of graphene oxide quantum dot inclusion to replace surfactants in a pickering emulsion intended to enhance the immune response to a Pgp3 recombinant vaccine against *Chlamydia trachomatis*[20]. The study reported no mucosal immune response in the lower genital tract. However, this study provides an interesting approach to future intravaginal drug administration by substituting surfactants, that can disrupt the vaginal microbiome, with nanocomposites offering superior biodegradability and biocompatibility. Moreover, the pickering emulsion was produced by a simple sonication method which is also beneficial for upscaling purposes[20].

7.4. Self-emulsifying drug delivery systems

The literature reports the development of SEDDSs for intravaginal application that have zeta potential changing behavior, enhanced self-emulsification capacity to enable spontaneous emulsification upon introduction to small vaginal fluid volumes and mucoadhesive properties[254]. Zeta potential changing SEDDSs developed by Nazir and co-workers, was achieved *via* a flip-flop mechanism. This mechanism improved mucus permeation and epithelial uptake by initially introducing SEDDSs harboring a highly negative zeta potential from surface hydrophilic phosphate substrates to accelerate mucosal permeation. Upon arriving at the epithelia phosphate substrates are cleaved by alkaline phosphatase rendering a "flip out" of amino substructures on oily droplet surfaces to amplify cellular uptake due to the slightly negative zeta potential change[254]. On the other hand, Köllner and co-workers reported curcumin containing SEDDSs having increased spreadability, mucosal permeation, and curcumin-protecting properties. These SEDDSs had slightly negative zeta potentials to mediate mucosal crossing of droplets larger than 200 nm[142]. Moreover, compared to a commercial O/W cream SEDDSs exhibited up to 68% mucosal coverage compared to 4% covered by the commercial cream. Swift spontaneous emulsification upon introduction to small fluid volumes by SEDDSs is imperative to ensure lipophilic drug release at mucosal surfaces[142]. Rohrer and co-workers evaluated 10 SEDDSs and concluded that a minimum final concentration of $\leq$40% diluted SEDDS will enable self-emulsification. Emulsification time can vary from 30 min to 30 s depending on SEDDS composition[152]. Thereby, signifying that rapid spontaneous emulsification in small fluid volumes makes SEDDSs a promising vehicle for transvaginal drug delivery. However, the literature also reports that prolonged exposure to surfactants can disrupt the gut microbiome leading to long-term health concerns[151]. Therefore, a study by Jirwankar and co-workers investigated the effect of spontaneous nanoemulsions on *Lactobacillus acidophilus* concluding that depending on the surfactant concentration growth retardation of this probiotic bacteria could be observed. Surfactants could be ordered as Capmul® MCM > Maisine® CC > Miglyol® 810>Kolliphor® RH40 to describe their cytotoxic impact and growth inhibition capacity[372].

7.5. Liquid crystals

Liquid crystals as self-assembled liquid composites are underexplored as a potential vaginal drug delivery vehicle. Jie and co-workers incorporated sinomenine also known as the main alkaloid component present in Qingfengteng, a Chinese herb, into liquid crystal gel to target cervical cancer, provide pain relief and reduce inflammation following vaginal administration[282]. Phytantriol, a well-known lyotropic liquid crystal material often utilized in personal care products, was included as the sinomenine-loading matrix. *In situ* cubic liquid crystal gels were developed exhibiting a gel transition time of 8.92 s within small vaginal fluid volumes. Moreover, *in vitro* release studies based on the dynamic dialysis bag method confirmed sinomenine hydrochloride sustained release ranging 144 h. Additionally, the *in vivo* experiments demonstrated that cubic liquid crystal gels were retained in vaginal mucosa of healthy adult female Sprague Dawley rats for longer than 12 h[282].

7.6. Eutectic systems

Limited studies have reported the application of deep eutectic systems or eutectic mixtures for vaginal administration. However, a single study reported investigating the possibility of a deep eutectic system formation between metronidazole and hydrophilic agents to enhance drug release *via* an enhanced dissolution rate in the presence of small fluid volumes[373]. This is an interesting concept as the idea is based on a non-mucoadhesive principle. The authors, therefore, suggested that the deep eutectic system should be incorporated into a solid vaginal insert to simplify handling and administration. Results indicated that metronidazole was released in a controlled fashion over a period of 7 days in simulated vaginal fluid. Thereby, signifying that deep eutectic systems capable of controlled release can effectively replace oral metronidazole therapy[373].

8. Clinical translation of liquid-based transmucosal drug delivery systems

Practical and ethical challenges often obscure academic innovations from reaching commercialization[374]. Therefore, despite the advances made to mediate the crossing of mucosal barriers, clinical translation of these dosage forms presents numerous obstacles to overcoming bench-to-bedside transitions. The seven steps of clinical translation refer to: (a) up-scaling potential, (b) standardized characterization procedures, (c) stability analysis, (d) mode of action, (e) establishing safe and effective drug doses, (f) Good Laboratory Practices (GLP) toxicity evaluations, and (g) clinical studies involving human subjects[374]. Academic innovations are generally not constrained by the seven steps of clinical translation[374]. Thereby, implying that many significant scientific discoveries remain academic knowledge instead of changing the lives of patients in clinical settings. In most cases, liquid-based drug delivery systems lack standardized protocols considering the efficacy and safety which hinders regulatory approval due to the limited availability of extensive data on toxicity for patients, researchers involved in dosage form development as well as the impact on the environment if numerous patients are consuming these systems due to factors such as increased surfactant content and nano-sized droplets[12,139,374–378]. In terms of scalability, nanoemuslion development remains challenging as minute process differences can drastically impact physicochemical properties[377]. Thus, compromising the safety and even quality of nano vehicles. The high-energy production methods of nanoemulsions also impede upscaling as it is not cost-

effective[377]. Apart from high-energy methods, the incorporation of surfactants can also negatively impact the long-term biological safety of these dosage forms[377].

It is understandable that SEDDSs have garnered significant scientific attention, as no high-energy production methods are required to produce these systems and upscaling is more realistic compared to nanoemulsions. Importantly, the stability challenges of liquid SEDDSs can be conquered by solidifying them *via* melt extrusion, freeze drying, and adsorption onto solid carriers[379–381]. This allows for the combining of liquid-based SEDDS advantages with the enhanced stability, simplified handling, and portability of solid dosage forms[139]. In terms of oral drug delivery, liquid-based systems can be administered by filling soft or hard gelatine capsules as is the case with Norvir® (ritonavir), Sandimmune® (cyclosporine), and Fortovase® (saquinavir), established on liquid-based formulations[139,382]. However, the authors suggest that the solidification of liquid-based drug delivery systems can be considered to allow reconstitution with a pre-determined water quantity prior to transmucosal administration to gain the advantages of localized liquid-based transmucosal drug delivery without compromising on dosage form stability. This can potentially simplify regulatory assessment and clinical translation of certain liquid-based dosage forms.

The literature reports numerous tools of optimization and characterization of ionic liquid-based systems[376,383–386]. However, the reproducibility of liquid-based drug delivery systems such as liquid crystals, ionic liquids, and eutectic mixtures also causes a delay in clinical translation of these systems[376,387–389]. This delay can be attributed to inadequate stability of formulations combined with the absence of clear guidelines for their stability. Moreover, the presence of potential impurities and unknown extent of biodistribution also hinder their commercialization[376]. Importantly, liquid crystals are also considered as a building block for nanoparticle formulation[390]. Therefore, the clinical translation of these liquid-based systems is also restricted due to the absence of standardized guidelines by the United States Food and Drug Administration (FDA), Central Drugs Standard Control Organization, India (CDSCO), European Medicines Agency (EMA) which are the main regulatory bodies responsible for the approval of nano-therapeutics before reaching the market[377]. It should also be emphasized that tuning and production of novel ionic liquid-based systems necessitates a cumulative understanding to consider the biological implications of these systems, as exceptional safety and targeted delivery should remain imperative before allowing these systems to reach the market[391]. Hence, due to the vast applications of ionic liquids in cancer, antimicrobial, adjuvant, and drug delivery innovations substantial validation of preclinical and clinical data is essential yet absent. Moreover, extrapolating data obtained from animal studies to humans also forms a complex part of clinical data collection due to interspecies variability[391]. Clinical translation of these systems is also handicapped due to the absence of standardized safety and efficacy protocols despite their reported superiority to marketed products[375]. As an example, a recent randomized controlled trial considering the delivery of ketoconazole incorporated into choline geranate formulations rendered superior treatment outcomes when compared to the commercially marketed product, Daktarin® [392]. Remarkably, the ionic liquid-based formulation incorporated a lower dose of ketoconazole while demonstrating superior efficacy to Daktarin® treatment of Tinea Pedis infection[392]. Thereby, signifying the potential of these systems despite their scarce commercialization.

9. Conclusions and prospects

Localized, targeted drug delivery approaches provide an important alternative to oral drug delivery as these innovative drug delivery approaches can compensate for poor pharmacokinetic properties such as limited aqueous solubility to ensure controlled drug delivery at target sites[73,357,393]. Mucosal surfaces provide unique challenges to drug delivery due to different dynamic physiological environments[176,268,356,394]. Despite the challenging mucosal surface environments, numerous advancements have been made regarding liquid-based drug delivery from anchoring to mucosal surfaces to mediating the crossing of mucosal barriers *via* innovative drug delivery approaches[165,170,176,269,364]. This review considered novel liquid-based drug delivery approaches involving nanoemulsions, SEDDSs, double-emulsions, phase-transforming liquid formulations, ionic liquid-based formulations, liquid crystals, and eutectic systems to cross mucosal surfaces. Although most of these drug delivery systems were first discovered during the last century, there is a scientific upsurge regarding liquid-based drug delivery systems, especially in terms of transmucosal drug delivery as liquids provide improved spreadability and adhesion at mucosal surfaces. Moreover, presenting a drug in solubilized form at mucosal surfaces can generate rapid uptake as the rate-limiting step of dissolution in small fluid volumes can be bypassed. Liquid-based drug delivery systems are also advancing due to innovative vaccine developments intended for mucosal administration or as vaccine adjuvants to generate mucosal immunity[20,31,94,223,320].

Another advantage of liquid-based drug delivery systems is the possibility of solidifying these vehicles to improve stability, prolong shelf-life, and simplify upscaling by subjecting formulations like SEDDSs to freeze drying, hot-melt extrusion, spray drying, wet granulation, and adsorption to solid carriers[380,382]. Another interesting future application for liquid-based drug delivery systems is to use liquid vehicles as materials for three-dimensional dosage form printing[297]. Recent advances in the deposition of liquids in orodispersible film development describe utilizing semi-solid formulations or liquids exhibiting high viscosity that are subjected to material extrusion to produce orodispersible films[297]. Additionally, recent fluid-based three-dimensional printing of contact lenses has also garnered scientific attention as contact lenses can provide sustained release in ophthalmic therapy[395]. Currently, gelatine methacrylate combined with PEG diacrylate or hyaluronic acid is the material of choice then processed *via* material extrusion to provide a base for anti-inflammatory, local antibiotic, and beta antagonist administration[297]. The main challenge here lies in creating biocompatible contact lenses without causing vison impairment[297].

Apart from three-dimensional dosage form printing, magneto-responsive ferrofluids are also emerging as colloidal suspensions harboring magnetic nanoparticles in an oil or water medium while stabilized against nanoparticle agglomeration by surfactant inclusion[396]. The magnetic manipulation potential of ferrofluids can especially benefit targeted drug delivery during cancer therapy. Limited studies report using ferrofluids in transmucosal dosage forms due to potential mucosal irritation. However, the literature does report the intranasal administration of magnetic nanoparticles and separate publications report utilizing ferrofluids during nanoparticle formulation to improve nanoparticle targeting capacity[397,398]. Moreover, a recent study reported the stabilization of a double-emulsion comprising ferrofluids by permanent magnet application[399]. Ferrofluids are also employed in liquid robotics as their morphology and multimodal locomotion can be controlled

via external stimuli to guide liquid-based drug delivery[400]. This review mentions the potential of ferrofluids as a future prospect for liquid-based drug delivery system development, but also contemplates that the material properties such as viscosity, polarity, and magnetic responsiveness of these systems can drastically impact up-scaling and long-term stability. Moreover, these magnetic fluid systems lack extensive safety evaluations, similar to more established liquid-based drug delivery systems, which implies that these systems are even further from successful clinical translation compared to dosage forms such as SEDDSs and eutectic systems.

The most notorious shortfall of liquid-based drug delivery systems is their slow progress regarding clinical translation despite advanced academic innovations. Hence, meaningful directions for future studies include comparing the efficacy of novel innovations to marketed products to demonstrate their superiority[392]. Moreover, one must bear in mind the importance of studies that evaluate the safety, toxicity, and environmental impact of liquid-based drug delivery systems as extensive data is needed to assist regulatory bodies such as the FDA, CDSCO, and EMA in establishing guidelines and protocols for their clinical translation.

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Author contributions

Daniélle van Staden: Writing - original draft, Writing, review and editing, Visualization, Project administration, Funding; Hendrik J.R. Lemmer: Writing - original draft, Writing, review and editing, Funding; Wilna Liebenberg: Writing - original draft, Writing, review and editing, Funding; Josias H. Hamman: Writing - original draft, Writing, review and editing, Conceptualization, Funding. All authors have read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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