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Review Article

Micelle-Loaded Oral Dissolvable Strips: A Novel Strategy to Enhance Bioavailability and Pharmacokinetics of Therapeutics

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Abstract

Background: This review examines the technology and therapeutic potential of oral dissolvable strips (ODS) loaded with micellized active pharmaceutical ingredients (APIs) for improved systemic drug delivery. Oral dissolvable strips (ODS) have emerged as a convenient and patient friendly route for drug delivery; however, many APIs exhibit poor aqueous solubility and stability, limiting their therapeutic efficiency. Micellar nanocarriers embedded in ODS can overcome these limitations by improving the solubility, stability, pharmacokinetics, and bioavailability.

Objective: This review evaluates the integration of micelle technology with ODS platforms to improve systemic absorption and therapeutic performance of APIs, focusing on formulation advances, pharmacokinetic improvements, and translational challenges.

Methods: Peer-reviewed research articles, patents, and reviews related to micellized APIs and oral film drug delivery systems were analyzed to identify formulation strategies, physicochemical optimization approaches, and clinical implications for diverse APIs.

Results: Micelle-embedded oral films enable efficient delivery of hydrophobic drugs, produce faster absorption and achieve higher plasma concentrations than conventional oral routes. By improving patient compliance, minimizing toxicity, and protecting APIs from hepatic and gastrointestinal degradation, micelle/ODS systems significantly enhance bioavailability. Challenges exist with formulation variables such as micelle composition and film thickness which affect release kinetics, and optimization and stabilization of micellized APIs.

Conclusion: Integrating micellar nanotechnology with oral dissolvable strips represents a promising next-generation platform for effective, non-invasive, and patient-compliant oral drug delivery. This technology holds great potential for delivering prescription drugs, supplements, chemotherapeutics, and biologics. Future investigations should prioritize optimizing formulation strategies and scalable manufacturing processes, clarifying regulatory pathways, and designing clinical trials.

Keywords: micelle, oral dissolvable strip, bioavailability, pharmacokinetics, drug delivery

INTRODUCTION

Oral drug delivery is a foundation of pharmacotherapy. This delivery system is distinguished by its non-invasive, convenient application and generally leads to a high level of patient compliance. However, oral drug delivery can be problematic for many active pharmaceutical compounds, especially those with poor aqueous solubility, low membrane permeability and compounds which may undergo substantial metabolic changes associated with first-pass metabolism. These issues are even more prominent in pediatric and geriatric populations as well as dysphagic patients, all of whom may have difficulty taking traditional tablets or capsules[1,2].

The broad category of oral thin films (OTF) has emerged as a promising and accepted method of delivering Active Pharmaceutical Ingredients (APIs) orally. In drug delivery, the API is the core component(s) of any drug that is responsible for producing the intended therapeutic effect. Essentially, it is the biologically active substance within a medication that is responsible for its therapeutic action, whether by treating the disease symptoms, preventing the disease or modifying physiological processes. Some drugs/medications may contain more than one APIs that act in different ways. Oral thin films deliver drugs primarily via oral mucosal absorption or gastrointestinal (GI) absorption, depending on how the product is designed. As mentioned, Oral thin films is a broad term, that encompasses both oral mucosal and gastrointestinal (GI) tract absorption methods.

Oral dissolvable strips (ODS) represent an advanced class of thin, polymer-based drug delivery systems designed to rapidly dissolve in the moist environment of the oral mucosa. Within the category of ODS, two subtypes can be differentiated based on placement of the ODS in the oral cavity and the absorption site. Oral dissolvable strips (ODS) or oral dissolvable films are designed to deliver medication through the oral mucosa directly into the bloodstream, bypassing the digestive system and the liver [1]. This results in a more rapid onset of therapeutic effects as well as higher bioavailability because the drug

avoids first-pass metabolism in the liver. ODS are further divided into buccal films, which are applied to the buccal mucosa until they dissolve and sublingual films which are placed under the tongue [1,3]. Both types of ODS provide for rapid release directly into the bloodstream as the buccal mucosa and especially the sublingual mucosa are highly vascularized, allowing for a quick absorption. For this reason, ODS or oromucosal strips are particularly fast acting, in addition to avoiding both first-pass metabolism and degradation in the stomach's acidic environment [3].

Buccal strips are typically applied to the inner lining of the cheek thus allowing the drug to be released and absorbed directly across the buccal mucosa. This route can also support sustained residence time on the oral mucosa if the films are mucoadhesive [4,5]. Sublingual strips are placed under the tongue, where the highly vascularized sublingual mucosa facilitates a more rapid systemic absorption and high bioavailability and is especially useful for drugs that require a fast therapeutic effect [4,6]. Taken together, buccal and sublingual ODS can be described as mucosal-targeted oral dissolvable systems. These are distinguished from orodispersible films or oral rapid-disintegrating films (ORDF) that primarily rely on GI absorption after dissolution in saliva, similar to traditional tablets and capsules and are widely used to improve compliance in pediatric and geriatric populations[7,8,9]. This distinction is critical in highlighting the unique pharmacokinetic and therapeutic opportunities of mucosal ODS platforms compared to ORDF.

ODS technology is designed for the thin polymeric matrices within the strip to dissolve rapidly in the oral mucosa, usually within 30-60 seconds, often with minimal to no water, and enable the majority of drug absorption to occur via the buccal or sublingual mucosa [4]. This approach has the great potential as the permeability of buccal mucosa is approximately 4-4,000 times greater than that of the skin [4,7]. Hence, a buccal or sublingual drug delivery system serves as an excellent vehicle for absorption of molecules, often leading to faster onset of action and increased bioavailability due to the circumvention of first pass metabolism [4]. As such, this review will focus on ODS technology as the primarily drug delivery system for review.

ODS technology, as advanced as it has become, is not without certain limitations. The drug-loading capacity on an ODS tends to be low, often less than 30 mg per strip [6]. In addition, the API on the strip must exhibit good solubility in saliva to ensure rapid dissolution, thus limiting ODS use for hydrophobic or poorly soluble drugs [7]. Further, ODS formulations are sensitive to moisture and can exhibit physical or chemical instability during storage [6,7]

Oral dissolvable strip (ODS) formulations also have formulation obstacles. Since the API or ODS components can sometimes have a bitter or unpleasant taste, a common challenge in ODS development is masking these to make the ODS more palatable [8]. Additionally, embedding APIs or subjecting films to production stresses can give rise to brittle or weak films, especially when heat-sensitive substances are involved [5,10]. Moreover, ODS preparation may exhibit defects such as residual solvents, trapped air bubbles, and film shrinkage [11,12]. Perhaps most importantly, it is difficult or often impossible to deliver drugs/APIs that are unstable at buccal pH or highly hydrophobic within an ODS matrix.

These limitations in ODS technology, especially drug solubility and loading, make ODS an ideal platform to pair with micellar nanocarriers for the API, which can encapsulate hydrophobic APIs, stabilize them and improve mucosal uptake. Micellization, a process by which there is a spontaneous self-assembly of amphiphilic molecules, above a critical concentration, in an aqueous media whereby the hydrophobic segments of the micelle cluster inward to form a core and the hydrophilic segments arrange outward forming a stabilizing shell. These nanostructures are referred to as micelles [13]. Micellar nanocarriers are among the most actively studied drug delivery platforms today. Their nanoscale core shell architecture enables encapsulation of hydrophobic drugs while maintaining colloidal stability in aqueous environments. Over time, several classes of micelles have been developed, each with their own strengths and trade-offs. In this review, we survey polymeric micelles, mixed micelles (polymeric–polymeric or lipid–polymeric), stimuli-responsive micelles, and targeted micelles, comparing their advantages and limitations.

As mentioned, the core shell allows micelles to solubilize hydrophobic and poorly water-soluble drugs by encapsulating them in the hydrophobic core as the hydrophilic exterior then maintains solubility and stability [14,15].Thus, micellization provides an extremely functional way in which lipophilic molecules, contained within nanosized carriers, can have increased solubility and be prevented from API precipitation during processing, thus improving overall stability of the structure. Placing APIs in micellar nanocarriers address some of the fundamental limitation of ODS. Micellization not only improves aqueous solubility but also stabilizes drugs against crystallization during film casting allowing for a higher effective drug dose to be loaded onto the ODS [16]. Mixed micelles, micelles formed from at least two different types of surfactant molecules have specifically been shown to enhance both solubility and oral bioavailability of poorly soluble compounds thereby expanding the range of drugs that can used with ODSs [17]. In fact, studies have confirmed that micellized APIs on ODS achieve significantly higher bioavailability compared to non-micellized controls, illustrating their value as a complementary technology to ODS [16,17,18].

Micelle types currently available for drug delivery include polymeric micelles, mixed micelles (both polymeric and lipid), stimuli-responsive micelles and targeted micelles. Among these micelle classes, polymeric and mixed micelles strike a balance between formulation, feasibility of use and functional performance when embedded into ODS. Polymeric and mixed micelle systems combine stability, solubility, and biological efficacy, making them currently the most used and best options for integration with oral dissolvable strip (ODS) technologies. Accordingly, this review focuses

on polymeric and mixed micelle systems, highlighting their advantages, limitations, and potential applications when embedded in ODS for prescription drugs, nutraceuticals, and chemotherapeutics. Stimuli-responsive and targeted micelles, while exciting, currently have many uncertainties such as stability, cost, regulatory and safety concerns which limit their reliable use for ODS embedding. As such, this review concentrates on polymeric and mixed micelles and examines how they can be formulated for optimal dissolvable strip delivery and the wide variety of uses for such a combination.

This review further focuses on technologies that integrate micelle-based carriers with ODS or thin dissolvable film platforms for the delivery of prescription medications, nutraceuticals and supplements, chemotherapeutic agents and biologics. Included are summarize comparative pharmacokinetic/absorption data in studies where micellized film/strip formulations are directly compared against non-micellized or conventional forms. This review also provides a review of some of the mechanistic insights into formulation strategies for micelle-ODS systems detailing micelle type, film/strip polymer selection, techniques for drug loading, and stabilization of both micelle and film matrix. Finally, this review discusses future research direction for this innovative technology to facilitate its successful translation into clinical use.

ORAL DISSOLVABLE STRIPS (ODS) IN DRUG DELIVERY

Oral drug delivery is a well-established and valid way in which to deliver drugs, supplements, vitamins and many other pharmacologic compounds to individuals. The most common formulations of tablets and capsules, however, can be inconvenient and require access to water. Additionally, tablets, capsules and even liquid formations are not really feasible for patients with many neurologic or muscular disorders [1,2] or groups such as pediatric, geriatric or diphasic populations characterized by swallowing difficulties or compliance [1,2]. As such there is a clear need for a more effective oral delivery system.

Oral dissolving strips (ODS) technology addresses the key limitations of conventional oral dosage routes offering faster and greater bioavailability and ensuring better patient compliance. ODSs are very slim polymer-based sheets designed to carry an active pharmaceutical ingredient (API). Once placed in the mouth, the film quickly dissolves allowing the API to be released directly across the oral mucosa directly into the bloodstream [19,20,21]. This route of administration enables drugs to bypass the gastrointestinal tract and first-pass hepatic metabolism, which can result in faster onset of therapeutic effect and enhanced systemic bioavailability.

ODSs are generally classified into two types, buccal films and sublingual films, based on the site of their application in the mouth. Buccal films are typically designed with mucoadhesive properties, adhering to the inner cheek and can provide either immediate or sustained drug release. Sublingual films, in contrast, dissolve beneath the tongue and enable rapid entry of the active agent into the systemic circulation through the highly vascular sublingual mucosa. Both formats ensure patient-friendly dosing and direct delivery of medication into the bloodstream.

Advantages and benefits of Oral Dissolvable Strip Technology

ODS technology offers several advantages over conventional oral dosage forms. The greatest benefit is the rapid release of the API which then drives a rapid onset of action. The films dissolve usually within 30 seconds after contact with saliva and API is then primarily absorbed via oral mucosa and as such can enter the systemic circulation more quickly than tablets, capsules or liquids which must be swallowed, metabolized and then absorbed in the gastrointestinal tract before the effect of the API can be felt [22]. ODSs also provide improved bioavailability for many drugs, since mucosal absorption can partially or fully bypass hepatic first-pass metabolism, leading to higher drug levels systemically and in some cases even facilitate a lower therapeutic dose of the API [23,24]. ODSs are generally well accepted by most individuals. They are thin, easily administered and can be used in a water-free environment which makes them extremely convenient. ODS is especially valuable for pediatric, geriatric, and any population where swallowing difficulties or dysphagia, nausea, or fear of choking might reduce patient compliance of traditional oral medications [19,25]. Additionally, ODS allow for delivery of a precise, pre-measured dose of the API which ensures a consistent pharmacological effect. For example, Ma et al, 2020 [23] investigated a sublingual ODSs containing the immunosuppressant everolimus, which is commonly used to prevent rejection of transplanted organs. They demonstrated a significantly higher bioavailability than oral solutions [23]. In other investigations it was shown that films containing the selective serotonin reuptake inhibitor, dapoxetine hydrochloride, improved systemic drug levels well as increased patient compliance [24]. There have been similar benefits with nutraceuticals and vitamins. ODS films loaded with the flavonoid luteolin, nearly double the blood concentration of an oral solution [26], and vitamin D3 loaded on an ODS demonstrated greater bioavailability than conventional oral formulations in healthy subjects [27]. Collectively, these findings affirm that ODS technology can not only overcomes the limitations of solubility, enzyme degradation, and first-pass metabolism seen in traditional oral dosage forms, but also deliver meaningful improvements in both pharmacokinetics and patient acceptability.

Finally, due to the solid and dry nature of films of the ODS, there is enhanced stability, especially compared with liquid formulations, and the nature of the ODS protects moisture-sensitive drugs potentially extending their shelf life [28].

Composition of Oral Dissolvable Strips

The exact formulation for the ODS vary depending on the intended use, however core ingredients typically include film-forming polymers, active pharmaceutical ingredients, plasticizers, flavoring ingredients, saliva

stimulating compounds, and sometimes coloring agents and/or disintegrants. Each of these components is described in more detail below.

Film forming polymers: The film forming polymers are the main structural component of the ODS and the most crucial components. These polymers directly impact the rate of active substance release and its compatibility with the membrane [5]. The polymers can be natural or synthetic. The most commonly use components in the natural category are Pullulan, gelatin, chitosan, hyaluronic acid, starch, gelatin, maltodextrins, pectin, and alginates [29]. The synthetic film forming polymers most commonly employed are Hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP), hydroxypropyl cellulose (HPC), and polyethylene glycol (PEG) [30]. While natural polymers are generally considered more favorable primarily due to perceived safety, natural film forming agents can be unstable. Recent studies have begun to combine multiple natural polymers [31] or use a composition of natural and synthetic film-forming components [32].

The Active pharmaceutical ingredients (APIs) are the active compound that is incorporated directly into the polymer matrix. APIs can include over-the-counter drugs, micronutrients, prescription medications, vitamins, or other supplements [25,33,34,35,36].

Plastizers: The primary function of the plasticizer component of an ODS is to improve the film's strength and flexibility and reduce its brittleness. Common plasticizers include glycerol, glycol, propylene glycol, and polyethylene glycol (PEG). It is important to note that the balance between plasticizers and film-forming agents has been shown to play a critical role in the final quality of ODS, thus emphasizing its importance of ODS design and manufacturing. For example, it has been shown that variations in the ratio of plasticizers and film forming polymers can directly influence the dissolution rate of the ODS [37]. Subsequent research has also highlighted that using combinations of plasticizers can enhance the mechanical properties of the strip and provide for a superior ODS. For example, Shojaee et al. (2020)[38] demonstrated that incorporating polyvinyl alcohol (PVA) with chitosan and plasticizing with both polyethylene glycol (PEG) and glycerol produced a synergistic effect. The combination of glycerol and PEG enhanced the elongation of break values by approximately five-fold compared to films plasticized with glycerol only. These findings highlight how polymer and plasticizer interactions can improve the mechanical stability of PVA/chitosan films, which may be valuable for pharmaceutical film applications, including oral dissolvable systems [38].

Sweeteners: Due to the fact that many ODS components themselves or the API loaded onto the ODS can taste bitter, the use of sweeteners is common. These are used to mask the unpleasant taste of active ingredients and enhance patient acceptability, especially for pediatric patients. Natural and synthetic sweeteners are currently used in ODS formulations to mask bitterness and improve palatability. Sweetener formulators use sucrose, glucose, or fructose, or sugar alcohols such as mannitol, sorbitol, xylitol, maltitol, and erythritol, or naturally sweet more intense sweeteners such as steviol glycosides (stevia) or thaumatin (Talin). Additionally, artificial sweeteners such as sucralose, saccharin, acesulfame K, and aspartame are used in ODS formulations, however, the preference is to use natural sweeteners. Comparative studies have shown that the type and amount of the sweetener can have impact on film dissolution time, film uniformity, and the tensile strength of the film [6,25]. Consequently, blends of natural, artificial, and high-intensity sweeteners are often used in order to optimize rapid disintegration, adequate mechanical stability, sweetness, and minimal aftertaste [7]. Abou-Taleb et al. (2022)[39] investigated three sweeteners, sorbitol, acesulfame K and sucralose on a vardenafil loaded oral dispersible film loaded with the drug vardenafil. They found that all three sweeteners had similar solubilizing capacity, but the sucralose and acesulfame K films offered notably better sweetness and palatability compared to the film using sorbitol [39].

Disintegrants: For oral dissolvable strips (ODSs) to be effective, the API must be released rapidly in the oral cavity. Most ODS are engineered to dissolve within about 30 seconds, due to their ultra-thin polymeric structure and the rapid hydration and disintegration of polymers that quickly facilitate disintegration upon hydration with saliva [5,19]. However, when higher API loading or a dense polymer matrix is necessary, this can slow down dissolution, and disintegrants, often referred to as superdisintegrants, may be incorporated into ODS systems to facilitate rapid disintegration without compromising film strength [40].

In ODS and orodispersible formulations, disintegrants accelerate breakup primarily through several key mechanisms referred to as wicking, swelling and deformation/strain recovery thereby speeding saliva penetration and dissolution of the film [7,40,41]. Their effectiveness depends on how rapidly the ODS disintegrates upon contact with saliva. Among the most important mechanisms driving this process are wicking and swelling, both of which are influenced by the presence and type of disintegrant incorporated into the film matrix.

Wicking refers to the capillary action by which hydrophilic disintegrant particles, such as crospovidone, croscarmellose sodium, or chitosan, draw saliva into microcapillary channels formed within the polymeric film. This facilitates a uniform moisturizing of the matrix and also accelerates the hydration and film breakup [40,41]. In this process, the liquid penetrates along the interfaces between polymer and disintegrant particles, effectively reducing the film's cohesion thus augmenting disintegration throughout the strip. Complementary to this, swelling may also occur when disintegrants such as croscarmellose sodium and chitosan are in the formulation as they absorb water and expand [42]. The resulting internal pressure generates mechanical stress within the hydrated film, which accelerates the film's rupture and detachment from the mucosal surface [42]. The combined action of wicking and swelling therefore

ensures both rapid disintegration and effective release of the active API for buccal or sublingual absorption.

Although these mechanisms were first established for tablet disintegration, they are increasingly recognized as applicable to thin film dosage forms [40,42].

While less relevant than in tablets, since ODS are not compressed solids, some disintegrants create micro-channels or porosity in the film during casting/drying. Upon hydration, in a process referred to as deformation, these channels can allow for penetration of fluid. Additionally, Alghaith et al. (2022) [43] demonstrated, in their development of a fast-dissolving flibanserin film, that cross-linked povidone could serve as an effective disintegrant exemplifying good physical and mechanical characteristics as well as an enhanced disintegration time.

Finally, there has been some research into the use of natural disintegrants such as starch, agar, and guar gum due to their non-toxic nature, however, the incorporation of these materials into ODSs often compromises the film uniformity and stability. Due to the highly absorbent nature of these compounds and their potential microbial degradation, the use of natural disintegrants in ODS formulations remain very limited [25,40].

Stabilizers and Thickeners in Oral Dissolving Strips (ODS): In oral dissolving strips (ODS), stabilizers and thickeners are essential components that help preserve the integrity, uniformity, and functionality of both the film matrix and API during the manufacturing, storage, and use of the ODS. Their primary roles include preventing API degradation, maintaining mechanical consistency, and ensuring uniform API distribution throughout the film.

Stabilizers, including pectin, cellulose derivatives, and antioxidants such as ascorbic acid and butylated hydroxytoluene (BHT) are commonly used to prevent oxidation and moisture-induced degradation of APIs [25,44]. Additionally, chelating agents such as ethylenediaminetetraacetic acid (EDTA) are commonly incorporated to inhibit metal ion catalyzed oxidation or degradation of the formulation's components, thus increasing the chemical stability of the film during storage [25]. Small amounts of cosolvents or surfactants, such as Tween 80, may also be incorporated to enhance miscibility, thus facilitating rapid dissolution and release of the API from the film matrix during use [41].

Thickeners used in preparation of ODS are generally high molecular weight polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), xanthan gum and pullulan, and are utilized to increase the viscosity of the casting solution, to improve mechanical strength and promote uniform drying, and minimize sedimentation of the API [41]. However, as noted above, too much viscosity can slow down the dissolution of the ODS, therefore ODS formulations must strike a balance between mechanical strength and rapid disintegration/dissolution [44]. For example, Cheng et al. (2021)[45] demonstrated that incorporating low concentrations of xanthan gum with pullulan effectively stabilized vitamin B12 within an ODS and maintained a mechanically stable ODS that was smooth in texture and palatable, while also keeping dissolution rapid at approximately 30 seconds. Thus, while stabilizers and thickeners are essential for maintaining ODS quality and performance, the proportions must be optimized.

Saliva-stimulating agents: Increased saliva not only accelerates film hydration and thus dissolution but also improves patient comfort and taste perception. These agents are typically acidic ingredients added to enhance film disintegration by stimulating the sour taste receptors on the tongue thus triggering the gustatory-salivary reflex which subsequently causes the salivary glands to produce more saliva [46]. Citric acid is the most widely used saliva stimulating agent, however other organic acidic compounds such as tartaric and malic acid have also been employed [6,25].

Coloring agents: These additives, while not functionally necessary, improve the visual appearance of the ODS and thus their appeal, which can enhance compliance, especially in pediatric patients. Natural colorants such as beta-carotene as well as synthetic dyes are used as coloring agents in ODSs [6,19].

There are multiple techniques for preparing ODSs which include solvent casting, hot melt extrusion, electrostatic spinning and spray, and 3D printing, however the manufacturing of the ODS is beyond the scope of this review.

Current uses for oral dissolvable strip and orodispersible film technology

ODS as well as orodispersible film technologies have already demonstrated clinical and commercial success across diverse therapeutic categories. They have been used in the delivery of medications for pain management, opioid-use disorders, mental health disorders, nausea, migraines, seizures, and antihistamine therapy**,** as well as nutraceutical and supplement formulations [35,47].

In the field of nutraceuticals and dietary supplements**,** both buccal and sublingual ODS and oral disintegrating strip formulations are marketed for their rapid onset and improved absorption. Common examples include strips containing vitamins B, C, and D_3**;** herbal extracts such as Ginkgo biloba, curcumin, and saffron; minerals like iron and magnesium; and bioactives such as melatonin, L-theanine, glutathione, caffeine, and probiotics [48,49,50]. Clinical studies have validated the use of orodispersible films loaded with cholecalciferol or vitamin D_3 and have demonstrated bioavailability comparable to or higher than oral solutions [27], and demonstrated sustained improvement in serum levels of cholecalciferol [50]. In mental health, orodispersible films for drugs such as antipsychotics and antidepressants have shown improved patient adherence and acceptability, particularly for individuals with swallowing difficulties [35].

Overall, oral dissolvable film technology which spans sublingual, buccal, and orodispersible films placed on the tongue, represent a versatile and patient-friendly platform that can be customized for either rapid mucosal absorption or systemic GI delivery. The platform utilized

depends on therapeutic goals and the physicochemical properties of the active compound. These technologies represent a highly flexible delivery system capable of accommodating a broad spectrum of low-dose APIs, supplements, and biologically active compounds.

MICELLER SYSTEMS IN DRUG DEVELOPMENT

Micelles are an assembly of nanoscale colloidal particles in which amphiphilic molecules self-organize into a hydrophobic core and a hydrophilic corona or shell that stabilizes the particles in an aqueous environment [15,51]. These nanostructures can encapsulate hydrophobic compounds and thus protect them from degradation and enhance their solubility in aqueous environments [52] (Figure 1) [53]. Several types of micelles have been developed, including polymeric micelles, lipid micelles and mixed micelles (both polymer/polymer and polymer/lipid).

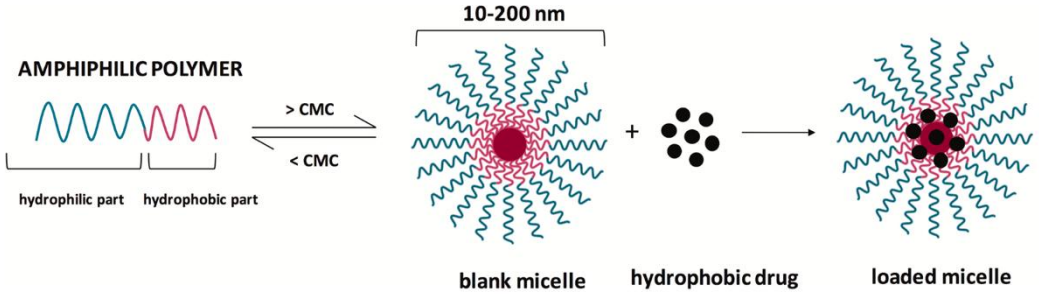

Figure 1: *Schematic representation of polymeric micelles.* Amphiphilic block copolymers self-assemble in aqueous environments to form micelles with a hydrophobic core and hydrophilic corona, enabling solubilization and delivery of poorly water-soluble drugs [53].

Reproduced from: Ghezzi M, Pescina S, Padula C, Santi P, Del Favero E, Cantù L, Nicoli S. Polymeric micelles in drug delivery: An insight of the techniques for their characterization and assessment in biorelevant conditions. J Controlled Release. 2021;332:312–336. © 2021 The Authors. Published by Elsevier B.V. under the Creative Commons CC BY 4.0 license.

In addition, while not the focus of the review, but included for completeness, there are also targeted micelles and stimuli-responsive micelles [54,55].

Targeted micelles have surface ligands, commonly utilizing antibodies or peptides, attached to the surface of the micelle steering the API loaded micelles to target specific cellular receptors and/or tissues, thus potentially improving the therapeutic index of the API [56,57]. These micelles are especially useful for chemotherapeutics [53]. The increased cost, complexities involved in creation, potential immunologic reaction as well as regulatory complexities remain a challenge for a more broad clinical use of targeted micelles.

Stimuli-responsive micelles are examples of triggered or controlled release micelles in which the API loaded micelle is responsive to triggers in the body such as pH, oxidation-reduction gradients, enzyme activity, temperature, or light [58,59,60]. These micelles are most commonly used for release in specific disease settings like tumor microenvironments where the pH or other properties are likely to be different from normal physiologic conditions. Unfortunately, stimuli responsive micelles can destabilize prematurely in the systemic circulation, can release the API at the wrong target, and/or they can be difficult to synthesize reproducibility [59,61]. Thus, despite their innovative design and therapeutic potential, both targeted and stimuli-responsive micelle systems have significant complexities that hinder their translation to the clinic, resulting in limited usage to date [59,61,62,63].

Among all micelles, polymeric and mixed micelles are the most widely investigated for pharmaceutical applications because of their enhanced stability, the ability to alter their size, and the superior drug-loading capacities compared to conventional surfactant systems [64,65,66]. Recent investigations further highlight polymer and lipid mixed micelles as the next-generation carriers of APIs, since the synergistic effects found when both polymers and lipids are combined can dramatically enhance drug delivery via the oral mucosa [64]. Thus, while there are multiple types of micelles currently being investigated regarding drug delivery, this review of combined micelle/ODS technology focuses on polymeric and mixed micelles as they provide the best foundation for integration into ODSs. The integration of this micelle technology into an oral dissolvable strip is a highly promising new method for drug delivery because it combines the benefits of each technology to enhance the bioavailability of poorly soluble drugs, enabling a more rapid and controlled drug release and increase bioavailability.

Polymeric micelles

Polymeric micelles are nanoscale self-assemblies of amphiphilic block copolymers, typically ranging from 10 -100 nm in diameter with excellent kinetic stability. Additionally, because it is critically important in drug delivery that the delivery vehicle, in this case a micelle, maintain structure even when diluted in the body, an optimal drug carrier must have a low critical micelle concentration (CMC), i.e. the concentration of surfactant in a solution at which self-assembly begins. Polymeric micelles generally exhibit relatively low critical micelle

concentrations, which allows for both their kinetic and thermodynamic stability in the body [67,68]. Furthermore, the amphiphilic block-copolymer design of polymeric micelles permits the modulation of micellar size, surface charge and drug-release kinetics thus allowing for specific delivery profiles based on therapeutic need [16]. Because of their ability to circulate in the body for extended periods, polymeric micelles have been widely studied for oral delivery and may offer great compatibility with film-based formats where maintaining film integrity is critical [14,15]. An illustrative example is the Soluplus® based amphiphilic polymeric micelle system which has been shown to substantially improve the oral bioavailability of poorly soluble compounds. In animal studies, Zeng et al 2017, in a study using scopoletin loaded Soluplus® micelles achieved a 4.38-fold increase in the total amount of the drug that reached the systemic circulation (AUC), and ~8.43-fold increase in is the maximum or peak concentration of a drug in the blood (C_{max}) compared with free scopoletin [69]. Soluplus® micellar systems are increasingly recognized for their utility in formulating BCS Class II/IV drugs for oral delivery [70].

Although polymeric micelles are excellent drug delivery carrier and a good platform for solubilizing poorly water-soluble drugs, they also have drawbacks. The drug loading capacity of polymer micelles is often moderate, and preparations require relatively complex synthesis and characterization steps which can be costly and difficult to scale. Additionally, while generally stable, variability in release kinetics and potential toxicity of certain polymers have limited the number of polymeric micelle formulations that have successfully transitioned to clinical use [53,71,72].

To address these challenges, mixed micelles, which are micelles composed of two or more amphiphilic molecules such as polymers and lipids/surfactants, have recently attracted much attention. By combining complementary components, mixed micelles can enhance colloidal stability, improve drug loading, and fine-tune the API release [67,73]. This synergistic approach allows mixed micelles to mitigate many of the limitations inherent in single-polymer systems, making them a more clinically translatable and potentially improving the pharmacokinetics of micelles [73].

Mixed Micelles (Polymeric + Polymeric or Polymeric + Lipid)

Mixed micelles, formed by blending different polymeric and/or lipid molecules together can create a novel micellar system that can utilize the most beneficial properties of each component. Mixed micelles are formed by combining two or more amphiphilic species, such as polymers with other polymers, or polymers with lipids/surfactants. This hybrid design utilizes the stability of polymers with the solubilization properties of lipids. Compared to single-component micelles, mixed micelles often show lower CMC values allowing for improved stability when diluted and exhibit the capacity for higher drug loading [74,75,76,77]. Additionally, polymer/lipid mixed micelles can enhance oral bioavailability by improving solubility in the mucosal transport pathways [17]. For example, lipid-polymer mixed micellar systems combining amphiphilic copolymers with P-glycoprotein-inhibitory surfactants have demonstrated the ability to suppress the efflux transporters and thus enhance intestinal drug absorption, indicating strong potential for embedding in orodispersible strip (ODS) platforms [65,78,79,80]. The versatility of mixed micelles also allows them to easily accommodate lipophilic or unstable API's that would not be stable if incorporated into thin film matrices.

In addition to their physical and chemical advantages, mixed micelles offer greater flexibility in customizing their API release profiles. By adjusting the ratios of the different components, mixed micelles can be optimized to deliver the API in a sustained release or rapid release manner depending on therapeutic need [58]. Mixed micelles also provide improved stability during storage and transport, which is essential for scaling commercial production [66]. Importantly, mixed micelles can incorporate targeting ligands or stimuli-responsive moieties without compromising overall stability, enabling targeting in diverse biological environments [81]. Finally, evidence suggests that combining polymeric and lipid elements can reduce the risk of premature leakage of the API therefore allowing for more controlled API release and potentially eliminating the toxicity of the carrier itself, thus addressing a common limitation of single-polymer micelles [73].

Collectively, these features make mixed micelles not only more versatile but also more clinically translatable, particularly for oral dissolvable strip (ODS) formulations where stability, bioavailability, and patient compliance are paramount.

Still there are drawbacks to mixed micelle technology. Reproducibility can be a challenge and there is additional complexity in scaling up their production. Additionally, since there are more variables in mixed micelles, the composition, ratio of components, and their interactions make mixed micelles more challenging to optimize.

Key Differences between micelles

Both polymeric and mixed micelles improve solubility and protect hydrophobic APIs, but their strengths are different. Polymeric micelles excel in stability, controlled release, and design flexibility[14,15], while mixed micelles offer superior solubilization, biological interactions, and compatibility with difficult APIs [17,73,76]. For ODS formulations, polymeric micelles contribute to film stability and controlled release, while mixed micelles address limitations in drug loading absorption.

Table 1: Comparative characteristics of polymeric, mixed polymeric, and polymer–lipid hybrid micelles.

Micelle Type	Typical Polymers / Components	Preparation Methods	Particle Size (nm)	Encapsulation Efficiency (EE%)	Therapeutic Examples	Ref
Polymeric Micelles	PEG-PLA, PEG-PCL, PEG-PPO, Soluplus®	Direct dissolution, dialysis, thin-film hydration, microfluidics	10–100	70–95%	Paclitaxel, Doxorubicin, Curcumin	15,82,83
Mixed Polymeric Micelles	PEG-PCL + Pluronic F127; Soluplus® + TPGS; PEG-PLA + chitosan	Solvent evaporation, thin-film hydration, microfluidics	20–120	75–98%	Ebastine, Scopoletin, Insulin peptides	84,85
Polymer–Lipid Hybrid Micelles	PEG-PLA + phosphatidylcholine; PCL + lecithin	Nanoprecipitation, emulsification-solvent evaporation	50–150	60–90%	Paclitaxel, siRNA, proteins	66,86

Notes: Values vary by preparation method; EE% = encapsulation efficiency. Reference numbers correspond to the reference list.

Key Advantages in Micellar Systems in Drug Delivery

Micellar nanocarriers provide several therapeutic advantages that address common barriers in oral and systemic drug delivery. The encapsulation of hydrophobic APIs within micellar cores enhances their solubility and dissolution rate, leading to improved bioavailability which is an especially useful strategy for drugs classified under BCS II and IV [87]. By encapsulating active pharmaceutical ingredients within their hydrophobic cores, micelles shield drugs from enzymatic and acidic degradation in the gastrointestinal tract and allow either sustained release or, in advanced formulations, stimuli-responsive release triggered by pH, temperature, or redox conditions [82,87]. Some micellar systems are also engineered with mucoadhesive properties that prolong residence at the oral or intestinal mucosa, while others reduce P-glycoprotein mediated efflux, thereby enhancing absorption of poorly permeable drugs [88]. The nanoscale size (~10–100 nm) of micellular systems has been shown to facilitate passive tumor accumulation through the enhanced permeability and retention effect, and "intelligent" micelles can further exploit the tumor microenvironment to trigger controlled drug release [82,87]. Importantly, micelles have shown particular promise in oral administration, as they protect labile or hydrophobic molecules during gastrointestinal transit, improve dissolution and permeability, and ultimately enhance the bioavailability. Collectively, these features underscore why micellar delivery platforms are increasingly regarded as versatile tools for improving therapeutic efficacy and patient compliance.

Table 2: Summary of micelle types used in drug delivery, highlighting their composition, advantages, challenges, and representative drug examples. Polymeric micelles and polymeric mixed micelles are of particular interest for integration with oral dissolvable strip (ODS) technologies due to their enhanced stability, drug loading, and potential to improve solubility and bioavailability of poorly soluble APIs. References are provided to illustrate seminal and representative studies across each micelle category.

Type of Micelle	Advantages	Challenges	Drug Examples	Ref
Polymeric Micelles	High stability, tunable size, prolonged circulation, controlled release	Requires precise polymer synthesis; sometimes slow drug release	Paclitaxel, Doxorubicin, Curcumin	82,89
Lipid (Mixed) Micelles	Enhance solubilization and absorption	Stability issues; limited drug loading	Cyclosporine A (Sandimmune®), Fat-soluble vitamins	90,91,92
Polymeric Mixed Micelles	Higher drug loading, stability, P-gp efflux inhibition, synergistic properties	Complexity in manufacturing; regulatory hurdles	Curcumin, Ebastine, Paclitaxel	73,93,94,95
Stimuli-Responsive Micelles	Targeted and controlled drug release; useful for tumors or inflamed tissue	More complex design; clinical validation needed	Doxorubicin (pH-responsive), Cisplatin (redox-responsive)	96,97
Targeted Micelles	Active targeting to tumors or receptors; reduces off-target effects	Expensive; requires complex conjugation chemistry	Folate-targeted doxorubicin micelles, Herceptin-tagged carriers	98,99

Preparation methods for Polymeric Micelles for Drug Delivery

As described, polymeric micelles are formed by amphiphilic block copolymers, which spontaneously organize into a core/shell structure in aqueous media. The hydrophobic core is capable of encapsulating poorly soluble drugs, while the hydrophilic shell, most commonly composed of polyethylene glycol (PEG), provides stabilization of the micelle and extends the circulation time of the micelle by minimizing protein adsorption and preventing recognition and clearance by the immune system [71,82,87,100]. Several preparation techniques are commonly employed for polymeric micelles.

The Dialysis method: The dialysis method is the most widely used polymer micelle preparation method in which the API and the polymer are co-dissolved in an organic solvent, commonly dimethylformamide or ethanol, then dialyzed against water, which removes the solvent and as the solvent diffuses out, micelles are spontaneously assembled [89]. It is simple, easily reproducible, and gentle as the process avoids harsh conditions that might degrade sensitive APIs. Additionally, the dialysis method produces small, uniform micelles with high drug loading efficiency, and the only significant limitation is that removing the organic solvent is time consuming [82,89].

Direct dissolution / solvent casting: Direct Dissolution is less commonly used, but also a simple process. The amphiphilic polymers and drug are dissolved in water or an aqueous media above the critical micelle concentration (CMC) thus forming micelles upon hydration [82]. The advantage to the direct dissolution method is that no organic solvents need to be used, however the lack of an organic solvent limits this process to APIs with at least partial water solubility and often result in low API loading capacities [82].

Solvent evaporation / thin-film hydration: The solvent evaporation method is also a common method used to make single polymer micelles. The process involves a polymer and API mixture which is dissolved in a volatile organic solvent, then evaporated to form a thin film, and subsequently hydrated to yield micelles [71]. This solvent evaporation thin film formulation is particularly suited for hydrophobic/lipophilic drugs, has a high entrapment efficiency and is scalable for manufacturing. Torchilin et al., (2007) emphasize that aggregation is a key limitation of this thin-film hydration methods because, unlike dialysis, hydration requires careful optimization [71]. If hydration conditions such as rate, temperature, pH, ionic strength, or the polymer/API ratio aren't carefully controlled, instead of uniform micelles, the resulting micelle formations can be unstable leading to clumped aggregates and reduced encapsulation of the API [71].

Freeze-drying / lyophilization: Freeze drying and lyophilization is typically combined with one of the above methods, most commonly dialysis or solvent evaporation, to create stable, solid micelle formulations that can be reconstituted before use [101]. Lyophilization / Freeze-Drying greatly enhances shelf-life of the micelle formulation, but the process adds an additional step [101].

Each method above can influence micelle size, drug loading efficiency and capacity, and stability. Optimization often involves balancing drug/API and polymer compatibility, polymer molecular weight, and processing conditions.

Preparation methods for Mixed Micelles for Drug Delivery

Mixed micelles are composed of at least two amphiphilic components, either two complementary polymers, polymer + polymer micelles, or a polymer combined with a lipid or surfactant, polymer + lipid micelles. By co-assembling these different amphiphiles, mixed micelles can give rise to an increased kinetic stability, a greater API loading capacity, and allow for greater control of the release of the API when compared with single-polymer micelles [84,85].

Polymer + Polymer Mixed Micelles: Polymer + polymer systems are typically prepared by the same methods used for single polymeric micelles, such as dialysis and thin-film hydration. In polymer + polymer systems, two distinct block copolymers, typically PEG–PLA with PEG–PCL, can modulate the balance between the hydrophilic and lipophilic components in the micelle allowing for improved encapsulation efficiency and a modifiable API release [84]. Dialysis, in particular, is generally preferred as it facilitates a gradual assembly of the polymers and API leading to uniform, stable micelles. As mentioned above for single polymeric micelle production, thin film hydration is scalable, but requires careful optimization of the hydration step in order to avoid inappropriate aggregation [75,85].

Polymer + Lipid Mixed Micelles: Polymer + lipid hybrids, commonly using phosphatidylcholine with PEG polymers, are commonly prepared using thin-film hydration or solvent evaporation. The process involves co-dissolving both the lipid and polymer in an organic solvent and then hydrating to form a mixed micelle product. One of the greatest advantages in this type of micelle is that the lipid component lowers the CMC for the micelle, improves the retention of the API, and reduces toxicity of the carrier which maintains biocompatibility [65]. This makes polymer + lipid mixed micelles particularly attractive for oral and mucosal delivery, where stability and controlled release are critical.

Other Methods Applicable to both types of mixed micelles: Direct Dissolution for mixed micelle preparation is applicable when at least one amphiphile is water-soluble. The advantage is that it is a solvent-free, and is an uncomplicated method, but the API loading capacity is often low and as such is only used in unique, uncommon situations [87,102].

Co-Precipitation/antisolvent precipitation with freeze-drying is primarily used for poorly soluble drugs where the API and amphiphiles are first dissolved in an organic solvent and this solution is rapidly mixed with a miscible antisolvent in which the API and carriers are not soluble

and they quickly precipitate out, forming micelles. Freeze-drying may be added to the process to improve stability and shelf life. While this process is applicable to both polymer + polymer and polymer + lipid systems, this method requires very careful optimization to ensure particle size and prevent aggregation [103].

In summary, the processing methods are largely shared between polymer + polymer and polymer + lipid mixed micelles, however the method of preparation is generally selected based on the physicochemical characteristics of the drug and the therapeutic objectives, rather than the type of mixed micelle.

INTEGRATION OF ODS AND MICELLE PLATFORMS

Oral dissolvable films, the thin polymeric films that dissolve rapidly within 30-60 seconds in the oral cavity via the tongue (lingual films) or via the buccal/sublingual mucosa, enable fast dissolution or disintegration in the oral cavity with absorption of active pharmaceutical ingredients (APIs). These delivery routes allow APIs to be absorbed either directly across the oral mucosa into systemic circulation or, in the case of lingual films, swallowed and absorbed via the gastrointestinal (GI) tract [19,104].

While both methods work very well to deliver drugs and other compounds to individuals via a palatable, convenient and pharmacologically advantageous method, conventional ODS/orodispersion film systems still face critical limitations such as API drug loading capacity and an inability to load poorly water-soluble or unstable APIs, both of which restrict the clinical effectiveness of the drug delivery system [20]. Combining these strip/film technologies with micelle technology substantially enhances the delivery of a diverse range of pharmaceuticals. Micelles improve the solubility, stability, and permeability of hydrophobic APIs, while the ODS/orodispersible film matrices enable convenient, non-invasive administration and in some cases mucosal absorption. Together, these systems can address poor API solubility, enhance drug loading, and extend the therapeutic potential of ODS/orodispersible film platforms. Thus, by combining micellar encapsulation with dissolvable film technology, micelle-loaded ODS can potentially overcome the formulation limitations of either system individually, and it can extend to biologics and peptides, where conventional oral routes are severely limited.

Incorporating micellar nanocarriers with ODS and orodispersible films significantly improves therapeutic performance by improving solubility, stability, and bioavailability of a wide range of APIs, especially lipophilic compounds [20,87]. Pioneering research in the feasibility of encapsulating an APIs into a micelle which could then be loaded onto ODS or oral dispersible films in lieu of loading a non micellized API has been investigated. Islam et al. (2021) used a mixed micelle system composed of Poloxamer 188 and TPGS-1000 and encapsulated the antihistamine ebastine, this micelle mixture was then loaded into an orodispersible sublingual film [94]. They observed a 2.18-fold increase in bioavailability relative to the non-micellized pure drug on their film formulation [94]. Similarly, in earlier work, Chou et al. (2020) fabricated lipid-core micelles loaded with insulin and rhodamine 123, which were then printed onto mucoadhesive buccal films [105]. In their *ex vivo* studies using porcine buccal mucosa, they demonstrated that the film-embedded micelles exhibited significantly higher permeation through the mucosa for both compounds as compared to micelles in suspension and free drug solutions [105]. Additionally, other formulations, such as nanoparticle or nanosuspension loaded films, further support the platform's ability to improve dissolution, buccal absorption, and pharmacokinetics for both small molecules and biologics [106,107].

In particular, embedding micelle nanocarriers into oral dissolvable strips (ODS) represents a promising innovation that combines the advantages of nanoscale drug delivery with the convenience of ODS administration. This hybrid platform can protect active pharmaceutical ingredients from degradation in the gastric environment and bypass first-pass metabolism, leading to a faster onset of action and improved systemic exposure and bioavailability, all while maintaining a high patient compliance and ease of use, which are the parameters characteristic of ODS [19,104]. Direct evidence supports this approach. Recently curcumin-loaded micelles formulated into sublingual ODS demonstrated improved solubility and bioavailability, confirming that micelle integration into ODS matrices can broaden therapeutic potential even for highly lipophilic compounds [108]. Perhaps one of the best examples of the versatility of nanosuspensions paired with ODS was shown by Elshafeey et al 2021 [109]. This group investigated the potent serotonin reuptake inhibitor, Paroxetine, which has a very bitter taste, low water solubility, and undergoes extensive first pass metabolism, all leading to poor oral bioavailability of less than 50%. Using a paroxetine nanosuspension embedded in oral dissolving film, they demonstrated an enhanced buccal permeation of threefold in their ex vivo permeation model and the relative bioavailability was found to be 178 % compared to tablets in their healthy human volunteers [109].

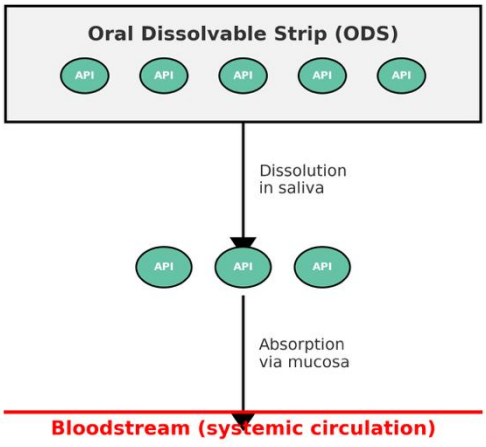

Figure 2: *Schematic representation of micelle-loaded oral dissolvable strips (ODS).* Active pharmaceutical ingredients (APIs) are encapsulated in micelles embedded within thin polymeric ODS films. When placed

in the oral cavity, the strip rapidly disintegrates in saliva, releasing API-loaded micelles. These micelles enhance solubility and mucosal absorption of poorly soluble APIs, enabling rapid entry into systemic circulation while bypassing first-pass hepatic metabolism. This approach combines the portability and compliance benefits of ODS with the bioavailability-enhancing properties of micellar nanocarriers. *Adapted from established concepts in micelle drug delivery and oral thin film technologies* [19,82,83,84]

Thus, integration of micellar nanocarriers into oral dissolvable strips (ODS) represents a promising advancement in drug delivery technology, combining the advantages of rapid oral mucosal absorption with the protective and functional properties of nanoscale micelle carriers.

Rationale and Formulation Strategy

Micelles can be pre-formed and incorporated into oral dissolvable strip (ODS) matrices via solvent-casting techniques, enabling uniform nanocarrier distribution while preserving micelle structure through casting and drying [94,105]. Film-forming polymers such as HPMC, pullulan, PVA, chitosan, and pectin are typically selected to balance ODS mechanical strength with rapid disintegration [8,110]. Plasticizers like glycerol or polyethylene glycol are added to enhance film flexibility, but their concentrations must be carefully optimized since excess plasticizer can destabilize micellar structure [43,111]. Additional formulation priorities for micelle-embedded ODS include preventing micelle aggregation or API expulsion during drying as well as maintaining dose uniformity per strip, given the inherently low drug-loading capacity typical of ODS [112,113,114]. Where extended drying is required, cryoprotectants such as trehalose and controlled temperature/humidity profiles can mitigate aggregation and preserve micelle dispersibility [111].

While adhesion to the buccal or sublingual mucosa, or mucoadhesion, is primarily conferred by the polymers in the ODS itself which interact with mucin primarily through hydrogen bonds and electrostatic interactions [115,116,117,118], micelles, which generally lack strong mucoadhesive properties, contribute primarily to solubility, stability, and enhanced permeability. However, the surface of micelles can be modified with cationic polymers to yield mucoadhesive properties. For example, thiolated-chitosan micelles showed a marked increase in mucosal adhesion, and other systems combining chitosan-derived amphiphiles also improved mucin-micelle interactions and inhibited P-glycoprotein (P-gp) efflux, thereby enhancing uptake and prolonging residence time at mucosal surfaces [119,120,121].

Advantages of Micelle-Loaded ODS

Integrating micellar nanocarriers into oral dissolvable strips (ODS) represents a significant advancement in oral drug delivery, combining the rapid onset and convenience of ODS with the solubilizing, protective, and targeting capabilities of nanoscale carriers. Both micelle/ODS and traditional orodispersible films can deliver low-dose therapeutics effectively; however, mucosal ODS systems offer a distinct pharmacokinetic advantage by enabling direct systemic absorption across the buccal or sublingual mucosa, thereby bypassing first-pass hepatic metabolism and avoiding degradation in the gastrointestinal tract. This pathway provides a faster onset of action, higher bioavailability, and reduced variability compared with orodispersible film in which the drug is swallowed and absorbed through the GI tract [19,104,108].

One of the key advantages of the micelle/ODS/orodispersible film platform lies in its ability to deliver both lipophilic small molecules, including chemotherapeutics with dose-limiting toxicity, and larger biomolecules such as insulin, which would otherwise be unstable or poorly absorbed through the GI route. Micelles also protect APIs from enzymatic and chemical degradation within saliva or gastric fluids while additionally offering controlled or stimuli-responsive release[122,123]. By embedding micelles into ODS matrices, APIs can be released in a predictable and sustained manner, overcoming one of the limitations of conventional ODS systems, which provide for rapid but uncontrolled API release.

Micelle-based ODS systems have also demonstrated clear benefits for nutraceuticals and natural compounds. For example, curcumin-loaded mixed micelle loaded onto sublingual films dissolved within approximately 40 seconds and achieved over a two-fold increase in bioavailability compared with the free compound [106]. Similarly, Soluplus® micelles significantly enhanced scopoletin's systemic exposure, confirming the capacity of polymeric micelles to improve oral bioavailability of poorly soluble compounds [69].

Beyond solubility enhancement and absorption efficiency, micelle and ODS systems can be engineered for controlled and targeted release. Stimuli-responsive micelles are designed to respond to local changes in pH, temperature, enzymatic activity, or redox gradients and these micelle systems can be embedded in ODS matrices to achieve site-specific delivery. This is particularly valuable for oncologic agents where a reduction in the patient's systemic exposure to the compound is critical [54,81]. The small size of the micelles (<100 nm) can enable a progressive accumulation in the tumor vascularized area via the enhanced permeability and retention effect [124,125].

Finally, this ODS delivery system is portable, discreet, and easy to administer making the combined technology particularly appealing for pediatric, geriatric, and dysphagic populations. When combined with micellar nanocarriers, ODS platforms provide not only convenience and compliance but also scientifically measurable pharmacokinetic advantages, offering a truly non-invasive yet potentially superior alternative to conventional oral or parenteral formulations.

Taken together, these features position micelle loaded ODS as a next-generation platform for both pharmaceuticals and nutraceuticals, capable of achieving therapeutic outcomes that are faster, safer, and more consistent than those of traditional orodispersible or tablet-based systems.

CHALLENGES AND FUTURE DIRECTIONS

Micelle-loaded oral dissolvable strips (ODS) represent a promising hybrid technology that unites the solubilizing and stabilizing properties of micelle nanocarriers with the rapid release, enhanced bioavailability and convenience of thin-film dosage forms. Collectively, studies have shown that ODS/micelle platform can improve solubility, enhances absorption, provides novel opportunities for controlled release, and facilitate non-invasive, convenient administration. By addressing systemic obstacles such as poor aqueous solubility, chemical instability, limited permeability, and efflux mechanisms, micelle embedded ODS systems show significant potentiality to advance the oral delivery of both conventional small molecules and emerging biologics. With further optimization and clinical validation, these systems hold the potential to redefine how many therapeutics are administered [9,109.121].

Expanding the Therapeutic Reach of ODS–Micelle Systems

For chemotherapeutic agents, micelle ODS systems offer a promising route to achieve targeted and controlled release, minimize systemic toxicity but also deliver high local drug concentrations at the site of the tumor. Similarly, biologics and peptides, traditionally restricted to injectable routes due to enzymatic degradation and poor permeability could be feasibly delivered through mucoadhesive micellar ODS systems, which protect these macromolecules and facilitate mucosal absorption.

With regard to nutraceutical and supplements, micelle integration enhances the solubility and bioavailability of poorly absorbed compounds such as curcumin, vitamin D_3, coenzyme Q10, and other lipophilic antioxidants, allowing ODS micelle systems to serve as convenient, fast-acting delivery platforms for both wellness and therapeutic products.

The integration of micellar nanocarriers into ODS technology represents a transformative step in drug delivery, with applications extending beyond conventional pharmaceuticals or supplements. For example, as an option for nicotine replacement therapy (NRT), micelle-loaded ODS formulations have the potential, compared to existing nicotine gums, pouches or lozenges, to provide for more rapid craving relief, faster onset of action, lower nicotine doses, and improved mucosal absorption and bioavailability, all of which are key features that may increase smoking cessation success rates.

Altogether, the ODS/micelle platform offers a unified solution for delivering a broad spectrum of active ingredients, from low-dose small molecules to large, complex biologics combining improved pharmacokinetics and API stability with superior patient compliance.

Despite the promise of the ODS/micelle platform, there are challenges. The relatively low drug-loading capacity for an API on films consistently restricts the application of the system to utilize only potent APIs or those APIs that are effective at lower doses. Additionally, many APIs, especially BCS Class II/IV, have poor aqueous solubility and as such, dispersing them evenly or solubilizing them within the polymer solution of the ODS before casting can be difficult as the APIs may precipitate during solvent evaporation, reducing their overall uniformity and bioavailability [126].

Micellar stability during ODS formation also presents a challenge. The polymer matrix of the ODS must remain stable and flexible when loaded with the API and APIs can sometimes disrupt ODS film forming properties causing a phase separation leading to brittle or sticky films [127].The process of solvent casting can also lead to limitations for micelle oral dissolvable strip systems. According to Hoffmann et al. (2011), long drying times, residual solvents and stresses during the casting process can adversely affect film quality and drug stability [19]. Heat and other conditions associated with drying the ODS often cause degradation of APIs, particularly peptides, biologics, and antioxidants [128,129,130]. Additionally, uneven drying can result in a non-uniform distribution of the API across the strip, and crystalline or poorly dispersed APIs may also cause the ODS films to become brittle or sticky [112, 131,132]. These issues can further reduce the stability of micelle-loaded ODS during packaging and shipping. Furthermore, when APIs on ODSs are exposed to moisture or temperature changes over time, there can be API aggregation, API leakage from the film matrix, or chemical degradation of the strip itself [112,133,134]. From a patient-perspective, bitterness, oral mucosal irritation, and undesirable texture remain barriers to compliance, and as such micelle-ODS formulations often need taste-masking or flavoring agents added [133]. In addition, transitioning from laboratory scale solvent casting to reproducible, industrial type production necessitates innovations in manufacturing methods such as continuous casting, multilayer film architectures, or 3D-printing of films [112,135].

Regulatory uncertainties further complicate the translation of ODS/micelle technology to clinical and commercial settings. The integration of oral dissolvable strips (ODS) with micellar nanocarriers occupy a regulatory ambiguous area between traditional oral dosage forms, such as tablets or capsules, and nanoparticle medicine or combination products, which are generally subject to more stringent safety, stability, and classification requirements [136,137,138]. Recent analyses highlight that these hybrid formulations often fall outside conventional pharmaceutical categories, as they involve both nanoscale drug carriers and film-based delivery devices [138]. Because no dedicated regulatory framework yet exists for nanocarrier and film combination systems, these technologies are evaluated under overlapping guidance for nanomedicines and combination products[138,139]. This raises questions about how such products should be classified, what preclinical toxicology and clinical safety data are required, and which standard would govern stability, pharmaceutical equivalence, and quality control.

These regulatory complexities underscore the need for early and active engagement with regulatory agencies during preclinical and formulation stages, ensuring

alignment on classification, CMC (chemistry, manufacturing, and controls) expectations, and long-term safety evaluation [135,136,137].

Another critical gap is clinical validation of this mode of drug delivery. Although studies have clearly demonstrated improved pharmacokinetics and mucosal permeation in preclinical models, clinical data involving humans remains very limited. Establishing safety standards, consistent reproducibility and therapeutic efficacy via well designed clinical trials will be essential to advance these innovative systems from the laboratory to practical medical treatment settings [72,140,141].

Looking forward, several directions are likely to accelerate progress of this innovative method of drug delivery. Formulation innovations need to focus on enhancing the drug loading capacity of the ODS while still preserving micelle integrity and maintaining ODS flexibility and rapid disintegration. Enhancing mucoadhesion and/or improving targeted or stimuli-responsive API release mechanisms could further optimize time in the buccal mucosa and targeting of specific areas within the body. The therapeutic capabilities of ODS/micelle formulations could expand if potency and stability can be optimized to be effective beyond small molecules to include larger compounds such as chemotherapeutics, vitamins, and other select biologics. Advanced manufacturing methods such as continuous casting, 3D printing, and multilayered ODS systems can provide a new laboratory prototype with potentially a better industrial production [112,133,142].

In summary, micelle-embedded ODS platforms are at an exciting scientific and drug delivery point in time, positioned to substantially improve therapeutic effectiveness and patient outcomes across a broad range of therapeutic application. The continued and future success of this innovative technology will depend on advances in formulation science, scalable manufacturing methods, a supportive and clear regulatory framework, and robust clinical validation. All of these advances will be needed in order to fully translate ODS/micelle systems from laboratory innovation to widely accessible, patient-centered therapies capable of reshaping oral drug delivery across diverse therapeutic indications.

CONCLUSION

Combining micellized active pharmaceutical ingredients (APIs) with oral dissolvable strip (ODS) technology offers an innovative and highly adaptable platform for drug delivery. This platform bridges the gap between the rapid onset of inhalation or injection and the convenience of oral administration. The preclinical and clinical pharmacokinetic evidence reviewed here underscores this technology's capacity to optimize therapeutic efficacy, enhance bioavailability, and improve patient compliance, marking a significant step toward the next generation of oral drug delivery systems.

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