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Exploring the potential of mucoadhesive buccal films in geriatric medicine

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ABSTRACT

As the global demographic shifts toward an aging society, the geriatric patient population is steadily increasing. These patients often suffer from comorbidities and require numerous oral medications, which can be especially challenging for dysphagic geriatric patients. Mucoadhesive buccal films (MBFs) seem promising and could reduce pill burden, simplify administration, and enable individualized drug therapy. This review aims to explore the age-related changes in the oral cavity and their impact on MBF delivery, including potential strategies to overcome these age-related barriers to drug delivery. It was observed that aging impacts the oral mucosa as well the properties of the saliva. There are several studies in the application of buccal films including the use of a wide range of permeation enhancers. The 3D printing of buccal films seems to introduce dosing flexibility to buccal film manufacturing.

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Introduction

As healthcare advancements contribute to increased life expectancy, the geriatric population is expanding at a faster rate compared to previous decades. The World Health Organization predicts that the number of geriatric adults (aged 60 years and older) will rise from 1 billion to 2.1 billion by 2050 [1]. The extended lifespan of adults is accompanied by a susceptibility to disease, a consequence of the accumulation of age-related damage at the cellular and molecular level [2,3]. The aging process causes deterioration of body functions, often worsening the function of organ systems at rates dependent on individual environmental and genetic influence [3,4].

Age-related changes to the body often lead to disability and comorbidities in geriatric populations [3]. Currently, the most prevalent method for treating these comorbidities involves the prescription of multiple solid and liquid oral dosage forms. Approximately, 60% of established small-molecule drug products are delivered through the oral route. Oral formulations dominate the global pharmaceutical market, accounting for roughly 90% of all formulations designed for human use [5].

While oral drug delivery is convenient and widely accepted, oral administration poses challenges for geriatric patients, particularly those afflicted with swallowing difficulties (dysphagia) [6,7]. Mucoadhesive buccal films (MBFs) present an alternative dosage form option. These films adhere to the inside of the cheek, facilitating a controlled drug release via the buccal mucosa to achieve systemic or local effects. Buccal films remove the need for swallowing, offering a significant benefit for dysphagic geriatric patients and improving treatment compliance. Furthermore, administering drugs via the buccal mucosa bypasses the hepatic 'first pass' metabolism and pre-systemic degradation associated with oral drug delivery, improving bioavailability, and reducing the overall exposure to the active ingredient [8]. An opportunity to tailor and optimize buccal film drug delivery is also made possible with the adoption and adapting of 3D printing in film manufacture. Personalized medicine and dosing are becoming more attractive as the importance of a patient's individual needs are recognized, rejecting the traditional 'one-size fits all' concept, and advancements in technology can now facilitate this [9,10].

The buccal mucosa is a promising site for drug delivery due to the vast number of blood vessels throughout the lamina propria, providing a rich arterial blood supply to the tissue. Combined with the hydrated environment, the buccal mucosa is ideal for the dissolution and permeation of drug molecules into the circulatory system [11]. More details about the oral cavity have been covered extensively [12–14]. However, it is crucial to recognize that age-related changes also influence the physiology and function of the saliva and buccal mucosa, presenting challenges for buccal film drug delivery.

This literature review aims to explore MBFs as an alternative and age-appropriate dosage form for geriatric therapy. To assess their suitability for geriatric patients, this review investigates age-related changes to the buccal mucosa and oral environment, considering how these changes affect buccal drug delivery. Additionally, the review examines methods to minimize and counteract the challenges posed by these age-related changes. Innovative solutions such as permeation enhancers, saliva stimulation and 3D printing are explored to optimize buccal drug delivery for geriatric patients.

Age-related changes in the oral cavity and their impact on mucoadhesive buccal film drug delivery

Aging impacts the structure and function of the buccal mucosa, similarly to other organs and tissues in the body. Among geriatric populations, thinning of the buccal epithelium, decreased cell density, and impaired tissue regeneration are observed [2]. Additionally, geriatric adults are more susceptible to experiencing xerostomia

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(dry mouth) or salivary gland hypofunction [15]. These age-related morphological changes could impact the predicted performance of MBF drug delivery. To accurately predict, enhance and optimize drug delivery, age-related changes to the oral environment must be considered. A summary of age-related changes to saliva is shown in Table 1. It is worth noting that recruiting healthy geriatric subjects, without any morbidities, for clinical studies is difficult due to normal aging processes and age-related susceptibility [34]. However, some studies excluded subjects with conditions known to alter saliva secretion and those taking medications that induce xerostomia [18,19,32]. While this approach may account for certain variables, it limits the applicability of the findings [35]. To ensure clinical studies are truly representative of the population, it is beneficial to include geriatric patients with comorbidities, particularly those affecting the oral cavity. This would provide a more accurate understanding of the challenges and dynamics within this specific patient group, ultimately leading to more effective and inclusive therapeutic strategies.

Age-related changes to the oral cavity reduce the effectiveness of MBF drug delivery by reducing drug absorption across the buccal mucosa. These physiological changes necessitate considerations when designing MBFs intended for geriatric therapy, prioritizing features which promote improved drug delivery. In addition to age, gender and ethnicity also have an impact on saliva flow rate [36]. However, as this work is focused on geriatric drug delivery, only the impact of age has been thoroughly explored.

Age-related changes on the buccal mucosa

Limited studies have explored age-related changes to the buccal mucosa in geriatric populations and the resulting effect on buccal permeability. Although literature regarding buccal epithelium thickness in geriatric patients is scarce, intra-oral ultra-sonographic images highlight a general trend of buccal epithelium thinning as individuals age [37]. Research also highlights an increase in buccal epithelial cell size and a decrease in their sphericity [2]. The reduction in buccal mucosa thickness results in a shortened diffusion path for drug molecules, enhancing the drug permeation rate [38].

With increased age, a decrease in microvasculature within buccal mucosa is observed, with compromised vascular functions diminishing systemic blood circulation and consequently lowering drug distribution to tissues [39]. Diminished buccal microvasculature can present due to lifestyle factors or oral health conditions [40]. Furthermore, these age-related structural changes to the buccal mucosa contribute to impaired mucosal healing [39].

Mucus is a viscoelastic hydrogel formed by weak non-covalent bonds, facilitating carbohydrate–carbohydrate and interchain hydrophobic interactions. This creates a barrier between the buccal mucosa and MBF. Chloride and calcium ions present in mucus are responsible for the expansion of cross-linked mucin chains after secretion [41,42]. A study by Raynal et al. [42] identified the role of calcium ions in mucin condensation by promoting the aggregation of mucin molecules into large linear and branched structures, suggesting that the rheological properties of mucus are dependent on ion-mediated interactions. Therefore, like the saliva, increased ion concentrations could alter the rheological properties of mucus, increasing the viscosity and reducing the rate of drug diffusion from MBFs [43]. Aging has been observed to impact ion concentration; however, more research is required on the wide range of ions present in mucus and their concentration effects on drug absorption.

Table 1. Age related changes to saliva quantity, quality, and features.

		Age related changes		
		Adults	Geriatric	References
Buccal saliva film thickness (μm)		31.40–58.50		[16,17]
Flow rate (mL/min)	Unstimulated saliva	0.16–1.66	0.13–0.55	[17–24]
	Stimulated saliva	0.95–2.47	0.62–1.52	[17,18,20,21,23,25]
pH	Unstimulated saliva	6.06–6.97	5.44–7.32	[17,22,26–29]
	Stimulated saliva	6.29–7.40	5.80–8.15	[17,26,28–30]
Inorganic component concentration (mmol/L)	Na^+	5.64–7.00	6.80 ± 0.88	[19,31]
	K^+	13.47–18.80	25.45–25.90	[19,31,32]
	Cl^-	22.83–23.26	32.13 ± 5.00	[19]
	Phosphate	1.54 ± 0.01	2.66 ± 0.16	[19]
	Ca^{2+}	0.95–1.55	0.74–1.95	[19,24,31]
Organic component concentration (mg/mL)	Total protein	0.45–11.35	0.86–12.04	[16,19,25,32,33]
Extensional rheology (spinnbarkeit) (mm)		2.20–23.09	5.59 ± 0.99	[25,33]
Viscoelastic relaxation time (ms)		1.00	77.50	[32]

The two comparison groups include adult (18–60 years) and geriatric (>60 years) populations.

The impact of aging on the composition of saliva

As an individual age, physiological and environmental changes to saliva and the tissue of the salivary glands can occur. The volume of parenchymal tissue decreases, with the space occupied by non-functioning adipose and fibrous tissue, resulting in the reduction of protein production. Additionally, the composition of saliva changes, therefore affecting the composition of the contact layer between the dosage form and buccal epithelium [36].

The overall concentration of salivary components was significantly higher in the geriatric adults, compared to younger adults (Table 1). Although the function of salivatory glands is inhibited, the concentrations of the saliva components increase. Evidence indicates the water secretion pathway is inhibited, reducing the amount of water that makes up the saliva, resulting in a more concentrated saliva [19]. The increased salivary component concentration, especially mucin, in geriatric adults leads to the alteration of saliva's rheology [44]. The altered saliva viscosity increases the boundary layer thickness, decreasing the diffusion coefficient and reducing drug diffusion rates from MBF [45].

The impact of aging on salivary flow rate and pH

Saliva is produced by three pairs of major salivary glands (the parotids, submandibulars, and sublinguals) and hundreds of minor salivary glands. The saliva is then secreted directly into the oral cavity via ducts crossing the epithelium [46]. The flow of saliva can become a barrier to MBF drug absorption due to the occurrence of 'saliva wash-out' effect caused by salivary flux. Saliva continuously 'washes' the buccal mucosa and consequently dilutes the concentration of drug at the MBF contact site and simultaneously reduces the contact time of the formulation [47]. A study by Serpe

et al. [48] observed that significant backwash of sulforhodamine deposited into porcine mucosal tissue was caused by the dynamic flow of saliva. However, the washing effect of saliva can be reduced by the implementation of an insoluble backing layer, which is usually a drug free layer protecting the drug loaded layer from the saliva. This additional layer promotes a unilateral drug movement in addition to reducing the loss of drug in the saliva, and down into the gastrointestinal tract [48].

Reduction of salivary flow rate is a result of age-related changes within the salivary gland. A loss of mucous acinar cell volume and secretory tissue, accompanied with an increase of adiposity, is suspected to contribute to salivary gland hypofunction which can lead to xerostomia [20]. In geriatric adults, decreased salivary flow impacts the oromucosal drug delivery from MBFs. The reduced salivary flow creates a 'dry' oral environment, which can reduce the rate of drug dissolution from a film and its mucoadhesion to the buccal mucosa [49–51].

Additionally, a reduced salivary flow rate in geriatric adults affects the component concentration of the saliva which decreases the pH of the oral environment [50]. Drug molecules containing hydrogen accepting groups become ionized in more acidic environments, reducing their lipophilicity which directly hinders permeation across the buccal mucosa membrane [50]. A change in pH of the saliva and surrounding environment can hinder the mucoadhesion between the MBF and buccal mucosa by affecting the structural ionizable groups responsible for adhesion [52]. Mucoadhesive force influences the residence time of the MBF and is necessary for controlled and extended drug release [53].

The impact of medications on saliva secretions

Polypharmacy is a recognized and inevitable challenge experienced by many geriatric adults. Over 1000 drugs in 42 drug categories and 56 sub-categories are known to induce salivary hypofunction and dryness of the buccal mucous membranes [54]. Anticholinergic medications (including cardiovascular, antiemetic, and selective serotonin reuptake inhibitor/serotonin–norepinephrine reuptake inhibitor antidepressants) bind to muscarinic receptors situated in the oral salivary glands which inhibit acetylcholine pathways in the central nervous system, consequently reducing salivary flow [55,56].

Additionally, literature indicates that diuretic treatment (commonly prescribed for conditions such as hypertension, renal diseases, and cardiac failure) is associated with a decrease in salivary flow rate, pH, sodium, and calcium ion concentrations present in saliva in addition to a decrease in salivary buffering capacity [57]. The mechanism behind how diuretics influence salivary flow rate remains unclear; however, Nederfors et al. [58] hypothesize that salivary hypofunction induced by diuretics could result from the accumulation of diuretics in the lumen fluid, leading to inhibition of transportation proteins or dehydration due to excessive urinary excretion, ultimately reducing the volume of saliva produced. Due to prevalence of polypharmacy, there is a considerable likelihood that a geriatric patient may be prescribed more than one anticholinergic or diuretic agent. This scenario increases the cumulative burden, further worsening salivary hypofunction [2,37–40,55–57].

Features of mucoadhesive buccal film drug delivery system

Oral dosage forms remain the most popular treatment option in geriatric therapy due to their cost-effectiveness and scalable bulk manufacture. However, conditions such as dysphagia hinder oral drug delivery in this population [59,60]. Mucoadhesive film drug delivery presents a promising alternative for dysphagic geriatric patients, utilizing the rich vascularization and permeability of the buccal mucosa to deliver drug in a pH-stable environment, circumventing the swallowing challenges associated with traditional oral dosage forms [61]. Mucoadhesive films are thin, flexible, multilayered systems designed for prolonged drug release via the buccal mucosa. These films utilize a blend of mucoadhesive polymers to facilitate strong mucoadhesion, optimal mechanical properties, and prolonged drug release profiles [14]. To enhance flexibility, plasticizers such as glycerol, propylene glycol, and polyethylene glycol, are incorporated into formulation [62]. This flexibility allows films to adapt to the natural movements of the mouth, improving comfort and promoting patient acceptability. Mucoadhesive buccal films are particularly advantageous for geriatric patients as they are easy to administer, requiring simple insertion and adhesion to the buccal mucosa to facilitate the systemic drug delivery. In contrast, rectal, vaginal, and inhalation therapies demand higher cognitive and manual dexterity, which can be challenging for geriatric patients due to age-related physical and mental decline [63–65].

Alternatively, mucoadhesive buccal tablets are designed to remain fixed between the gum and cheek to deliver drug to the buccal mucosa. Similar to MBFs, buccal tablets rely on mucoadhesive polymers to facilitate strong mucoadhesion and prolonged drug release [66]. However, their placement limits the available contact surface area for mucoadhesion whereas the dimensions of MBFs are only limited by the surface area of the buccal mucosa. Unlike buccal films, buccal tablets do not contain plasticizers, leading to a more rigid formulation that may cause discomfort for patients during prolonged drug delivery. While this is a predictable drawback, sensory studies comparing the patient acceptability of MBFs and tablets are needed to confirm this.

Although buccal tablets are more prevalent in the market, buccal films offer underutilized advantages, such as reduced thickness and greater flexibility within the oral cavity, enhancing patient comfort [14,67,68]. Despite the lack of clinical research, the design of MBFs can prioritize patient-centric features and acceptability. A thinner, more flexible MBF reduces discomfort experienced by patients and strong mucoadhesion reduces the risk of detachment; these combined features result in improved patient compliance [67,68]. Table 2 summarizes the features MBFs investigated in literature, focusing on diseases more prevalent in geriatric population [1]. However, it is worth noting that geriatric populations have an increased risk of irritation of the oral mucosa [78]. Therefore, future studies exploring the relationship between aging and acceptability of MBFs have the potential to identify the impact of increased sensitivity of the oral mucosa on the success of MBF drug delivery.

These studies demonstrate film thickness between 0.02 and 1.34 mm, mucoadhesive forces between 0.05 and 63.60 N and retention times (also an indication of mucoadhesion) from 0.4 to 9.1 h. Folding endurance is an indication of film flexibility and is performed by folding the film until a break or tear appears. Table 2 indicates that these films exceed 100 folds. An appropriate thickness for MBFs is between 0.05 and 1.00 mm; however, there is not a universally accepted mucoadhesive or folding endurance criteria [79].

A limitation of MBFs is their relatively low drug loading capacity, constrained by the smaller surface area of the buccal mucosa [81]. Table 2 indicates a dose loading range of 0.17–70.00 mg, although the study by Gayathri and Jayakumari [80] reported a 500 mg loading of glipizide, albeit with significantly heavier films. The impact of buccal film weight on patients' acceptability remains unknown. Despite reduced drug loading compared to other dosage forms, buccal films benefit from bypassing gastrointestinal

Table 2. Application of mucoadhesive buccal films for treating diseases common in geriatric populations based on literature.

		Physical characteristics				*In vitro* evaluation		*Ex vivo* evaluation					
Disease	Drug	Drug dose (mg)	Film weight (mg)	Film thickness (mm)	Folding endurance (number of folds)	Maximum drug release (%)	Drug release duration (h)	Maximum drug permeation (%)	Drug permeation duration (h)	Mucoadhesion (N)	Retention time (h)	Application	Reference
Chronic obstructive pulmonary disease	Salbutamol sulphate	1.42	65.00–68.00	0.65–0.70	>300	53–99	8.0	–	–	0.46–0.51	–	Treatment of asthma associated with chronic obstructive lung disease and asthmatic disorders	[69]
		10.00	65.23–117.92	0.23–0.59	240–>300	>80	1.5	97–98	2.0–2.5	–	1.7–1.8	Relief of bronchospasm associated with asthma, chronic obstructive lung disease, and asthmatic disorders	[16]
Chronic Pain	Tramadol	1.68	14.35–21.48	0.11–0.18	>300	100	0.3–1.0	–	–	0.07–0.14	–	Treatment of acute and chronic pain (moderate to severe intensity), joint, muscle, wound, postoperative, or orthopedic injury induced pain.	[17]
		5.54	31.10–50.10	0.24–0.54	238–298	70–90	12.0	–	–	–	–	Prolonged treatment of pain after surgery or orthopedic injury.	[21]
	Fentanyl	1.28	66.40–83.20	0.67–0.80	–	95	0.3–1.0	5–25	8.0	–	–	Treatment of chronic and breakthrough pain experienced by cancer patients.	[22]
Dementia	Rivastigmine	12.00	–	–	–	88–110	10.0–24.0	-	–	0.05–3.59	–	Treatment of Alzheimer's disease and mild to moderate dementia associated with Parkinson's disease.	[23]
Depression	Duloxetine	15.00	10.78–66.94	0.14–1.12	–	78–99	2.0	–	–	–	–	Treatment of depression, generalized anxiety disorder and relives peripheral neuropathy and fibromyalgia pain	[24]
Diabetes	Insulin	0.17–2.88	–	0.02	–	>70	5.0	–	–	–	–	Reduction of blood glucose levels in diabetic patients	[70]
	Glibenclamide	12.00	24.24–34.10	0.19–0.34	221–292	61–84	8.0	53–68	8.0	0.07–0.25	8.2–9.1	Treatment of type 2 diabetes	[25]
		2.50	22.25–39.83	0.21–0.49	174–275	45–91	4.0	65–83	4.0	–	–	Treatment of maturity-onset diabetes as hypoglycemic agent	[26]
		10.00	153.18–200.12	0.20–0.62	>300	91–98	12.0	84	12.0	15.00–35.00	–	Treatment of type 2 diabetes	[27]
		2.50	23.40–121.50	0.10–0.28	–	79–94	3.5–6.0	–	–	4.37–11.38	–	Treatment of type 2 diabetes	[43]
	Glipizide	5.00	56.00–84.00	0.25–0.28	165–290	70–93	6.0	78–89	10.0	–	–	Treatment of type 2 diabetes by evoking pancreatic secretion of insulin in diabetic patients	[28]
		500.00	4860.00–5310.00	0.22–0.32	252–315	30–80	4.0	–	–	–	–	Treatment of type 2 diabetes by evoking pancreatic secretion of insulin in diabetic patients	[29]
	Sitagliptin	2.70	25.30–29.80	0.32–0.40	240–285	62–100	6.0–8.0	–	–	–	5.3–8.0	Treatment of type 2 diabetes	[30]

(*Continued*)

Table 2. Continued.

		Physical characteristics				*In vitro* evaluation		*Ex vivo* evaluation					
Disease	Drug	Drug dose (mg)	Film weight (mg)	Film thickness (mm)	Folding endurance (number of folds)	Maximum drug release (%)	Drug release duration (h)	Maximum drug permeation (%)	Drug permeation duration (h)	Mucoadhesion (N)	Retention time (h)	Application	Reference
Hypertension	Enalapril maleate	20.00	58.00–86.00	0.15–0.22	166–287	79–96	2.0	82–91	10.0	–	–	Treatment of high blood pressure and angina pectoris	[31]
	Propranolol hydrochloride	30.00	–	0.60	–	95–100	0.5	–	–	–	–	Treatment of cardiovascular diseases such as hypertension, arrhythmias. Additional application includes treatment of anxiety, migraines, and tremors.	[33]
		20.00	–	–	–	100	1.0–4.0	–	–	–	–	Treatment of cardiovascular diseases such as hypertension, arrhythmias. Additional application includes treatment of anxiety, migraines, and tremors.	[71]
Osteoarthritis	Diclofenac sodium	20.00	48.10–125.60	0.31–0.66	>300	67–99	6.0	–	–	–	–	Relieve inflammatory pain and reduce inflammation associated with arthritis	[63]
	Meloxicam	9.82	–	–	–	40–105	3.0	–	–	0.12–0.87	–	Treatment of inflammatory joint disorders	[72]
	Piroxicam	10.00	43.94–68.45	0.11–0.24	256–297	80–95	8.0	85	8.0	–	–	Treatment of inflammation associated with osteoarthritis	[72]
	Prednisolone	2.00	–	0.19–0.32	–	71–96	5.0–8.0	60	12.0	0.61–1.65	2.7–8.4	Treatment of inflammation associated with chronic inflammatory diseases	[73]
Periodontitis	Ibuprofen	35.00–70.01	–	0.52–0.91	–	100	4.0	–	–	0.19–0.54	2.0–6.5	Treatment of oral disease by providing anti-inflammatory and analgesic therapy in oral cavity	[74]
	Tenoxicam	2.00	–	0.56–1.02	–	50–100	1.0–7.0	–	–	–	–	Treatment of inflammation associated with chronic periodontitis	[75]
Xerostomia	Adipic acid	10.00–20.00	–	–	–	100	0.5	–	–	–	–	Treatment of xerostomia by increasing salivary flow rate	[76]
		20.00	67.15 ± 0.54	1.34 ± 0.02	>100	46–92	8.0	–	–	0.11–0.26	–	Treatment of xerostomia by increasing salivary flow rate	[77]

degradation and hepatic first-pass metabolism enabling therapeutic effects with smaller drug doses [81].

Permeation enhancers as an approach to enhance buccal drug delivery

The oral mucosal membrane is an important barrier to buccal drug delivery, acting as a rate limiting step for permeation across the buccal membrane. Permeation enhancers (Table 3) aid the transport of drugs across the buccal mucosa membrane, thereby enhancing bioavailability. Despite the shared objective, each permeation enhancer employs diverse mechanisms of action to achieve enhanced permeation. Table 3 highlights that compounds which act by the removal or disruption of buccal membrane lipids exhibit the greatest permeation enhancement. Incorporating permeation enhancers in MBF formulation is beneficial for geriatric patients due to the age-related physiological changes in the oral cavity which hinder effective drug absorption across the buccal mucosa. Permeation enhancers facilitate drug absorption across the buccal mucosa by modifying mucosal barrier properties and utilizing these excipients can improve and enhance MBF drug delivery for geriatric patients.

Lipid based permeation enhancement

Nonionic surfactants

Surfactants possess transcellular perturbation action, a proposed mechanism of action which involves the insertion of the surfactant monomer into the plasma membrane. The surfactant monomers remove phospholipids from the structure to form a mixed surfactant and phospholipid micelle [109]. The destabilization compromises the integrity of the plasma membrane which also raises concerns for toxicity.

Surfactants have been successfully employed in research pertaining to buccal drug delivery (Table 3) [110,111]. Nonionic molecules are more desirable for pharmaceutic formulations as the molecular structure can be altered to obtain a desired HLB – hydrophile–lipophile balance. Higher HLB values indicate a greater hydrophilicity and a HLB value between 12 and 14 being ideal to solubilize proteins in buccal membranes [70,110,111].

Fatty acids

The precise mechanism of action of fatty acids as permeation enhancers is not currently well defined. The proposed mechanisms include increasing the fluidity of mucosal membranes via extraction of buccal barrier lipids [87]. Literature indicates that fatty acid concentration, chain length, and degree of unsaturation (double bonds) contribute to the effectiveness of the permeation enhancer. The maximum permeation effect is achieved at an optimal concentration, and permeation declines as concentration increases further. The optimal concentration is also fatty acid molecule dependant as increase in chain length demonstrates a parabolic relationship to permeation enhancement factor (Table 3), with medium chain lengths (10 carbons) being the optimum [87,112]. Furthermore, buccal permeation increases when a fatty acid molecule contains more double bonds. Capric acid, a medium chain length fatty acid exhibits the largest enhancement of permeability compared to other fatty acids. This is likely attributable to capric acid's high lipophilicity, as indicated by its Log*P* value of 4.09 [87]. These findings suggest the efficacy of fatty acids in enhancing buccal permeation is dependent on the molecules ability to penetrate the buccal mucosa to interact with the lipid domains.

Bile salts

Bile salts are ionic amphiphilic compounds, characterized by both hydrophilic head groups and hydrophobic tails. Above the critical micelle concentration (CMC), they form micelles, which are essential for their role in drug delivery [91]. The mechanism of permeation enhancement is believed to occur through the solubilization and micellar entrapment of intercellular lipids, as well as the denaturation and extraction of proteins, which create hydrophilic channels in the buccal mucosal membrane [91]. As shown in Table 3, trihydroxy bile salts, such as sodium taurocholate, demonstrate greater permeation enhancement compared to dihydroxy bile salts. This suggests that the additional hydroxyl group in trihydroxy bile salts plays a critical role in enhancing their permeation effectiveness.

Another key mechanism of action for bile salts is the reduction of mucus viscosity and elasticity via breakdown of mucus structure [113]. This is particularly beneficial for geriatric patients, whose mucus viscosity and elasticity often increase, creating a barrier to drug delivery. By incorporating bile salts into buccal films, the age-related challenges to drug absorption can be overcome, improving the rate of drug diffusion across the mucosal layer and enhancing therapeutic efficacy for older populations.

Tight junction permeation enhancement

Cyclodextrins

Cyclodextrins are oligosaccharide molecules possessing a hydrophobic internal environment and a hydrophilic surface. Cyclodextrins are a recent addition to known permeation enhancers, and consequently research is scarce [114,115]. Methylated cyclodextrins exhibits the most significant enhancement in permeation across porcine buccal epithelium compared to other cyclodextrins [71]. Histological studies revealed that methylated cyclodextrin induced extended detachment of the superficial layers, indicating the opening of tight junctions within the membrane [71].

Chelators

The use of chelating agents to enhance buccal drug permeation is underexplored in research, with a singular study investigating the permeation enhancement of a chelator, citric acid, within a buccal film formulation, highlighting a notable research gap [100]. Calcium chelators act by depleting calcium ion concentrations, causing disruption of actin filaments and calcium dependant adhesion molecules to cause loosening of the tight junctions. Although chelators did not improve buccal drug permeation, research suggests calcium chelators have improved permeability of bovine cornea [100,116]. The lack of research is potentially due to the associated *in vitro* toxicity accompanied by the enhanced permeation [117–119]. Additionally, the current quantities of chelators used in research in buccal, ocular, and oral drug delivery exceed the limits permitted by FDA (0.1–0.01% w/v) [116,118]. These strict restrictions further emphasize the toxicity associated with chelators as permeation enhancers. Given their toxicological concerns, chelators may not be the most suitable option for use in MBFs, which rely on extended adherence to the oral mucosa for sustained drug delivery.

Table 3. Application of permeation enhancers used in buccal drug permeation studies.

Category	Mechanism of action	Permeation enhancer	Concentration (% w/w)	Drug	Dosage form	Enhancement ratio	Permeation flux (μg/cm² h)	Permeability coefficient (cm/h)	Reference
Surfactant	Disaggregation of lipids present in the epithelial membrane, loosening the mucous membrane barrier structure [72].	Brij 58®	1.00	Naltrexone	Solution	7.70	–	$14.0 \pm 2.0 \times 10^{-2}$	[72]
		Polyoxyethylene-2-stearyl ether	5.00	Triamcinolone acetonide	Gel	1.35	20.50 ± 2.1	–	[73]
		Polyoxyethylene-23-lauryl ether	5.00	Triamcinolone acetonide	Gel	1.13	17.44 ± 1.5	–	[73]
		Polyoxyethylene-2-oleyl ether	5.00	Triamcinolone acetonide	Gel	1.56	22.60 ± 2.2	–	[73]
		Tween 80®	–	Zolmitriptan	Film	1.59	305.15	–	[74]
			1.00	Timolol	Patch	–	33.00	–	[75]
			0.10	Naltrexone	Solution	0.70	–	$1.4 \pm 0.8 \times 10^{-2}$	[72]
			1.00	Naltrexone	Solution	0.30	–	$0.5 \pm 0.1 \times 10^{-2}$	[72]
		Tween 20®	30.00	Miconazole	Microemulsion	–	–	–	[76]
			35.00	Miconazole	Microemulsion	–	–	–	[76]
			40.00	Miconazole	Microemulsion	–	–	–	[76]
		Diethylene glycol	5.00	Triamcinolone acetonide	Gel	1.18	17.16 ± 1.4	–	[73]
		Sodium dodecyl sulfate	0.05	Caffeine	Solution	1.57	–	–	[77]
			0.10	Caffeine	Solution	1.63	–	–	[77]
			1.00	Caffeine	Solution	–	–	$3.24 \pm 0.53 \times 10^{-2}$	[82]
			1.00	Caffeine	Solution	1.81	2.37 ± 0.41	–	[77]
			0.05	Estradiol	Suspension	0.94	–	–	[77]
			0.10	Estradiol	Suspension	0.80	–	–	[77]
			1.00	Estradiol	Suspension	0.57	0.21 ± 0.08	–	[77]
			1.00	Mannitol	Solution	–	–	$6.41 \pm 3.17 \times 10^{-3}$	[83]
			1.00	Mannitol	Solution	–	–	$5.22 \pm 3.40 \times 10^{-3}$	[83]
			1.00	Nicotine	Solution	–	–	0.11 ± 0.03	[83]
			1.00	Nicotine	Solution	–	–	$3.40 \pm 1.25 \times 10^{-2}$	[83]
Glycols	Extraction of membrane lipids and proteins, increasing fluidization of lipids. Increase drug partitioning and solubility. Alteration of drug thermodynamic activity [84]	Diethylene glycol	5.00	Triamcinolone acetonide	Gel	1.18	17.16 ± 1.4	–	[73]
		Poly(ethylene glycol)	0.50	Didanosine	Solution	1.63	295.94 ± 15.24	$1.48 \pm 0.07 \times 10^{-2}$	[85]
			0.50	Tenofovir	Solution	1.30	132.82 ± 9.95	$6.60 \pm 0.40 \times 10^{-3}$	[85]
		Propylene glycol	–	Enhanced efavirenz (EFV)	Film	–	–	–	[86]
			–	Zolmitriptan	Film	1.85	323.53	–	[74]
		Tetraethylene glycol	5.00	Triamcinolone acetonide	Gel	1.18	17.16 ± 1.4	–	[73]

(*Continued*)

Table 3. Continued.

Category	Mechanism of action	Permeation enhancer	Concentration (% w/w)	Drug	Dosage form	Enhancement ratio	Permeation flux (μg/cm^2 h)	Permeability coefficient (cm/h)	Reference
Fatty acids	Increase of mucosal membrane fluidity by destabilizing the mucosal membrane via cholesterol dissolution or destabilizing the lipid packing [87]	Capric acid	1.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	61.00	6.73 ± 1.21	33.66 ± 6.03 × 10^4	[87]
			5.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	103.20	11.39 ± 3.72	56.96 ± 18.59 × 10^4	[87]
			10.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	147.70	16.31 ± 1.38	81.54 ± 6.92 × 10^4	[87]
			10.00	Fluorescein isothiocyanate labeled dextran. 20 Da Mw	Solution	5.00	0.13 ± 0.06	0.64 ± 0.29 × 10^{-4}	[88]
		Caproic acid	1.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	1.40	0.16 ± 0.06	0.79 ± 0.28 × 10^4	[87]
			5.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	1.00	0.11 ± 0.02	0.56 ± 0.11 × 10^4	[87]
			10.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	1.20	0.13 ± 0.04	0.64 ± 0.18 × 10^4	[87]
		Caprylic acid	1.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	1.10	0.13 ± 0.04	0.63 ± 0.22 × 10^4	[87]
			5.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	0.50	0.05 ± 0.02	0.26 ± 0.09 × 10^4	[87]
			10.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	15.10	1.67 ± 1.21	8.36 ± 1.02 × 10^4	[87]
			10.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	219.00	13.36 ± 1.96	66.78 ± 9.78 × 10^{-4}	[88]
			10.00	Fluorescein isothiocyanate labeled dextran. 20 kDa Mw	Solution	171.00	4.24 ± 0.47	21.22 ± 2.37 × 10^{-4}	[88]
			10.00	Fluorescein isothiocyanate labeled dextran. 40 kDa Mw	Solution	68.00	1.10 ± 0.07	5.49 ± 0.35 × 10^{-4}	[88]
			10.00	Fluorescein isothiocyanate labeled dextran. 70 kDa Mw	Solution	–	0.80 ± 0.03	3.99 ± 0.13 × 10^{-4}	[88]
			10.00	Fluorescein isothiocyanate labeled dextran. 150 kDa Mw	Solution	–	0.59 ± 0.06	2.95 ± 0.29 × 10^{-4}	[88]
		Dimethyl sulphoxide	5.00	Salbutamol sulphate	Patch	1.08	–	0.54 ± 7.20	[89]
		Isopropyl myristate	5.00	Salbutamol sulphate	Patch	2.17	–	1.08 ± 3.6	[89]

(*Continued*)

Table 3. Continued.

Category	Mechanism of action	Permeation enhancer	Concentration (% w/w)	Drug	Dosage form	Enhancement ratio	Permeation flux (μg/cm² h)	Permeability coefficient (cm/h)	Reference
		Lauric acid	1.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	2.70	0.30 ± 0.06	$1.51 \pm 0.32 \times 10^{4}$	[87]
			5.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	103.80	11.45 ± 1.81	$57.21 \pm 9.05 \times 10^{4}$	[87]
			10.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	93.70	10.35 ± 0.82	$51.73 \pm 4.09 \times 10^{4}$	[87]
			5.00	Fluorescein isothiocyanate labeled dextran. 20 kDa Mw	Solution	16.00	0.39 ± 0.14	$1.93 \pm 0.69 \times 10^{-4}$	[88]
		Levulinic acid	5.50	Caffeine	Solution	–	–	$3.62 \pm 0.85 \times 10^{-2}$	[82]
			5.50	Diazepam	Solution	–	–	$1.66 \pm 0.15 \times 10^{-2}$	[82]
		Linoleic acid	0.50	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	15.90	1.76 ± 0.64	$8.79 \pm 1.31 \times 10^{4}$	[87]
			1.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	10.30	1.14 ± 0.57	$5.71 \pm 2.85 \times 10^{4}$	[87]
			5.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	3.00	0.33 ± 0.13	$1.64 \pm 0.67 \times 10^{4}$	[87]
			10.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	3.90	0.43 ± 0.06	$2.14 \pm 0.32 \times 10^{4}$	[87]
			5.00	Salbutamol sulphate	Patch	4.33	–	2.15 ± 10.80	[89]
		Linolenic acid	1.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	4.30	0.47 ± 0.14	$2.35 \pm 0.68 \times 10^{4}$	[87]
			5.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	12.70	1.40 ± 0.26	$6.99 \pm 1.28 \times 10^{4}$	[87]
			10.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	17.40	1.92 ± 0.26	$9.60 \pm 1.29 \times 10^{4}$	[87]
			15.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	26.00	2.87 ± 0.51	$14.37 \pm 2.53 \times 10^{4}$	[87]
		Oleic acid	5.00	Caffeine	Solution	–	–	$4.25 \pm 1.29 \times 10^{-6}$	[82]
			5.00	Diazepam	Solution	–	–	$0.64 \pm 1.11 \times 10^{-6}$	[82]
			1.00	Didanosine	Gel	1.29	60.08 ± 10.34	$3.00 \pm 0.57 \times 10^{-3}$	[90]
			1.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	0.90	0.09 ± 0.04	$0.47 \pm 0.19 \times 10^{4}$	[87]
			5.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	4.10	0.45 ± 0.13	$2.77 \pm 0.53 \times 10^{4}$	[87]
			10.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	0.70	0.07 ± 0.01	$0.37 \pm 0.02 \times 10^{4}$	[87]
			5.00	Miconazole	Microemulsion	–	–	–	[76]
			10.00	Miconazole	Microemulsion	–	–	–	[76]

(*Continued*)

Table 3. Continued.

Category	Mechanism of action	Permeation enhancer	Concentration (% w/w)	Drug	Dosage form	Enhancement ratio	Permeation flux (μg/cm² h)	Permeability coefficient (cm/h)	Reference
			6.50	Miconazole	Microemulsion	–	–	–	[76]
			8.75	Miconazole	Microemulsion	–	–	–	[76]
			5.00	Salbutamol Sulphate	Patch	4.33	–	2.15 ± 7.20	[89]
		Oleodendrimer OA1A ester derivative ($C_{27}H_{49}NO_6$)	1.00	Didanosine	Gel	1.01	46.57 ± 4.93	$2.34 \pm 0.27 \times 10^{-3}$	[90]
		Oleodendrimer OA1ANa ($C_{27}H_{49}NNaO_6$)	1.00	Didanosine	Gel	1.72	80.30 ± 10.37	$4.01 \pm 0.57 \times 10^{-3}$	[90]
		Oleodendrimer OA1E ($C_{35}H_{65}NO_6$)	1.00	Didanosine	Gel	1.33	61.88 ± 9.75	$3.09 \pm 0.53 \times 10^{-3}$	[90]
		Oleic acid	1.00	Didanosine	Gel	1.29	60.08 ± 10.34	$3.00 \pm 0.57 \times 10^{-3}$	[90]
		Oleodendrimer OA1A ester derivative ($C_{27}H_{49}NO_6$)	1.00	Didanosine	Gel	1.01	46.57 ± 4.93	$2.34 \pm 0.27 \times 10^{-3}$	[90]
		Oleodendrimer OA1ANa ($C_{27}H_{49}NNaO_6$)	1.00	Didanosine	Gel	1.72	80.30 ± 10.37	$4.01 \pm 0.57 \times 10^{-3}$	[90]
		Stearic acid	1.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	1.00	0.04 ± 0.04	$0.58 \pm 0.19 \times 10^{4}$	[87]
			5.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	0.80	0.09 ± 0.02	$0.43 \pm 0.10 \times 10^{4}$	[87]
			10.00	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	0.80	0.09 ± 0.03	$0.45 \pm 0.13 \times 10^{4}$	[87]
Bile salts	Extraction of proteins and lipids in cell membranes, increasing membrane fluidity and creation of aqueous channels. Producing reverse micelles, creating hydrophilic pores in the cell membrane. Reducing viscosity and elasticity of mucus layer [91].	Sodium cholate	5.00	Triamcinolone acetonide	Gel	1.48	20.98 ± 2.0	–	[73]
		Sodium deoxycholate	5.00	Triamcinolone acetonide	Gel	1.74	25.21 ± 2.6	–	[73]
		Sodium glycocholate	4.00	Verapamil hydrochloride	Patch	–	–	–	[92]
		Sodium taurocholate	5.38	Fluorescein isothiocyanate labeled dextran. 4 kDa Mw	Solution	96.00	5.84 ± 1.01	$29.21 \pm 5.06 \times 10^{-4}$	[88]
			5.38	Fluorescein isothiocyanate labeled dextran. 20 kDa Mw	Solution	48.00	1.20 ± 0.21	$5.99 \pm 1.34 \times 10^{-4}$	[88]
			5.38	Fluorescein isothiocyanate labeled dextran. 40 kDa Mw	Solution	49.00	0.80 ± 0.05	$4.00 \pm 0.26 \times 10^{-4}$	[88]
			5.38	Fluorescein isothiocyanate labeled dextran. 70 kDa Mw	Solution	–	0.46 ± 0.04	$2.29 \pm 0.22 \times 10^{-4}$	[88]

(*Continued*)

Table 3. Continued.

Category	Mechanism of action	Permeation enhancer	Concentration (% w/w)	Drug	Dosage form	Enhancement ratio	Permeation flux (μg/cm^2 h)	Permeability coefficient (cm/h)	Reference
			5.38	Fluorescein isothiocyanate labeled dextran. 150 kDa Mw	Solution	–	0.40 ± 0.03	2.01 ± 0.15 × 10^{-4}	[88]
			0.50	Ondansetron	Tablet	2.81	5.23	–	[93]
		Sodium taurodeoxycholate	5.00	Mannitol	Solution	15.00	–	0.06 ± 0.04	[83]
			5.00	Mannitol	Solution	33.00	–	0.13 ± 0.03	[83]
			5.00	Nicotine	Solution	–	–	0.13 ± 0.02	[83]
			5.00	Nicotine	Solution	–	–	0.11 ± 0.02	[83]
			5.00	Triamcinolone acetonide	Gel	1.57	21.85 ± 2.2	–	[73]
Cyclodextrins	Derivative cyclodextrins are suspected to destabilize tight junction in mucous membranes, improving the absorption of drugs via the paracellular pathway [94].	β-Cyclodextrin	0.03	Omeprazole	Solution	1.10	2.38 ± 0.19	7.72 ± 0.13 × 10^{-3}	[95]
			5.00	Piroxicam	Tablet	–	1.17 ± 0.44	0.21 ± 0.08 × 10^{-3}	[71]
			5.00	Piroxicam	Tablet	–	3.02 ± 0.68	0.51 ± 0.14 × 10^{-3}	[71]
		β-Cyclodextrin-epichlorohydrin polymer	–	Clonazepam	Tablet	–	–	–	[96]
		Hydroxypropyl-β-cyclodextrin	8.00	Carvedilol	Tablet	–	22.00	–	[97]
			5.00	Piroxicam	Tablet	–	1.17 ± 0.44	0.21 ± 0.08 × 10^{-3}	[71]
			5.00	Piroxicam	Tablet	–	3.02 ± 0.68	0.51 ± 0.14 × 10^{-3}	[71]
			0.05	Ropinirole	Tablet	1.23	21.40 ± 0.78	4.20 ± 0.74 × 10^{-2}	[98]
		Methyl-β-cyclodextrin	–	Clonazepam	Tablet	4.60	19.20	16.70 × 10^{-3}	[96]
			0.03	Omeprazole	Tablet	1.40	2.69 ± 0.09	9.73 ± 0.04 × 10^{-3}	[95]
			5.00	Piroxicam	Tablet	–	2.41 ± 0.87	0.41 ± 0.12 × 10^{-3}	[71]
			5.00	Piroxicam	Tablet	–	7.78 ± 1.69	1.26 ± 0.35 × 10^{-3}	[71]
		Sulfobutyl ether-β-cyclodextrin	–	Clonazepam	Tablet	–	–	–	[96]
			0.05	Ropinirole	Tablet	1.28	22.60 ± 1.29	4.5 ± 0.25 × 10^{-2}	[98]
Chelators	Depletion of intracellular calcium ions causing loosening of tight junctions in mucous membranes, improving the absorption of drugs via the paracellular pathway [99]	Citric acid	5.38	Buspirone hydrochloride	Film	Did not enhance permeation			[100]
			8.00						
			9.33						
			5.38	Cetirizine dihydrochloride	Film	Did not enhance permeation			[100]
			8.00						

(*Continued*)

Table 3. Continued.

Category	Mechanism of action	Permeation enhancer	Concentration (% w/w)	Drug	Dosage form	Enhancement ratio	Permeation flux (μg/cm^2 h)	Permeability coefficient (cm/h)	Reference
			9.33						
Positively charged polymers	Ion pair interactions cause loosening of tight junctions in mucous membranes, improving the absorption of drugs via the paracellular pathway [101]	Chitosan	0.10	Metformin	Solution	–	32.48 ± 1.95	$1.05 \pm 0.07 \times 10^{-2}$	[102]
			0.50	Metformin	Solution	–	55.89 ± 3.08	$1.83 \pm 1.08 \times 10^{-2}$	[102]
			1.00	Metformin	Solution	–	50.22 ± 4.98	59.76 ± 0.00	[102]
			1.50	Metformin	Solution	–	41.52 ± 2.09	$1.30 \pm 0.05 \times 10^{-2}$	[102]
			2.00	Metformin	Solution	–	34.22 ± 2.60	$1.15 \pm 0.08 \times 10^{-2}$	[102]
			1.00	Celecoxib	Gel	–	0.66 ± 0.16	–	[103]
			2.00	Celecoxib	Gel	–	0.40 ± 0.00	–	[103]
			3.00	Celecoxib	Gel	–	0.25 ± 0.00	–	[103]
		N-trimethyl chitosan	0.05	Ropinirole	Tablet	1.34	24.46 ± 2.11	$4.80 \pm 0.74 \times 10^{-2}$	[98]
Other polymers		Carboxymethyl cellulose	0.50	Didanosine	Solution	0.75	136.45 ± 12.29	$0.68 \pm 0.06 \times 10^{-2}$	[85]
			0.50	Tenofovir	Solution	1.74	178.12 ± 12.87	$1.48 \pm 0.07 \times 10^{-2}$	[85]
		Poly(acrylic acid)	0.50	Didanosine	Solution	0.70	127.07 ± 7.30	$0.63 \pm 0.03 \times 10^{-2}$	[85]
			0.50	Tenofovir	Solution	1.56	158.80 ± 10.19	$0.79 \pm 0.05 \times 10^{-2}$	[85]
		Sodium alginate	0.50	Didanosine	Solution	0.99	179.61 ± 52.24	$0.90 \pm 0.26 \times 10^{-2}$	[85]
			0.50	Tenofovir	Solution	1.71	174.46 ± 66.56	$0.87 \pm 0.33 \times 10^{-2}$	[85]
Cell penetrating peptides	Bind to molecules and translocate plasma membranes [104]	Penetratin	2.70×10^{-4}	Salmon calcitonin	Solution	1.40	0.02 ± 0.01	–	[105]
			2.09×10^{-3}	Salmon calcitonin	Solution	3.40	0.05 ± 0.05	–	[105]
			4.19×10^{-3}	Salmon calcitonin	Solution	5.50	0.09 ± 0.01	–	[105]
Additional permeation enhancers		Aloe vera gel powder	0.26	Propranolol hydrochloride	Film	–	–	–	[106]
			0.26	Rizatriptan benzoate	Film	–	–	–	[106]
		Azone®	1.00	Celecoxib	Gel	–	0.43 ± 0.10	–	[103]
			2.00	Celecoxib	Gel	–	0.39 ± 0.11	–	[103]
			3.00	Celecoxib	Gel	–	0.87 ± 0.12		[103]
			56.3	Mannitol	Solution	–	–	$1.58 \pm 0.65 \times 10^{-3}$	[83]
			56.3	Nicotine	Solution	–	–	0.12 ± 0.01	[83]
		Citral	2.00	Simvastatin	Film	–	–	–	[107]
		Di-methyl sulphoxide	5.50	Mannitol	Solution	–	–	$2.05 \pm 0.79 \times 10^{-3}$	[83]
			5.50	Mannitol	Solution	–	–	$1.76 \pm 0.90 \times 10^{-3}$	[83]
			5.50	Nicotine	Solution	–	–	0.13 ± 0.04	[83]
			5.50	Nicotine	Solution	–	–	$77.40 \pm 8.35 \times 10^{-3}$	[83]
		Menthol	12.00	Verapamil hydrochloride	Patch	–	–	–	[92]
		Xylitol	0.01	Cystine	Film	10.60	52.33 ± 6.45	–	[108]

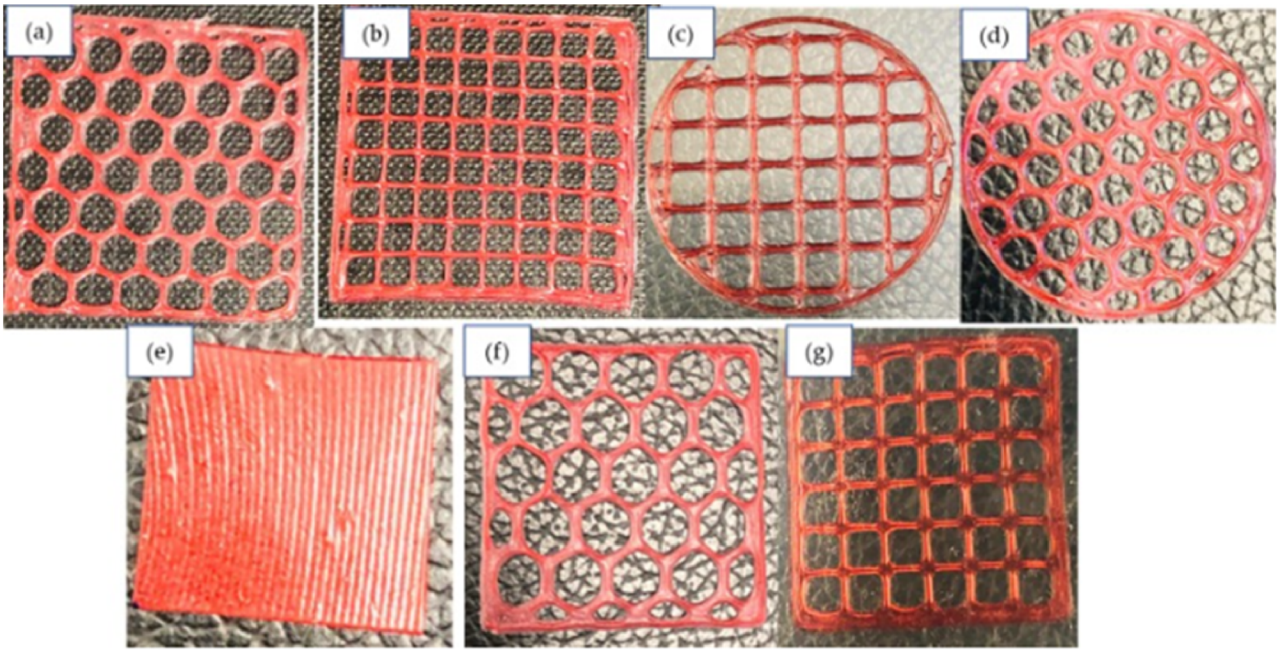

Figure 1. Digital photographs of 3D printed films with different shapes, infill patterns, and infill percentage. (a) Honeycomb infill (20%); 30 × 30 mm^2, (b) rectangular infill (20%); 30 × 30 mm^2, (c) rectangular infill (15%) (r = 16 mm), (d) honeycomb infill (20%) (r = 16), (e) plain infill (100%); 20 × 20 mm^2, (f) honeycomb infill (15%); 20 × 20 mm^2 rectangular infill, and (g) rectangular infill (15%), 20 × 20 mm^2 [133], with permission from international journal of pharmaceutics.

Positively charged polymers

The suspected mechanism by which positively changed polymers enhance mucosal membrane permeation involves the neutralization of the negatively charged interior of tight junction channels, loosening the pores; however, the mechanism is not entirely understood [120]. Negatively charged polymers can also improve mucosal permeability by altering tight junction function by chelating calcium [121]. However, their application in buccal mucosa permeation studies is less prominent, likely due to the potential toxicity associated with chelation, as discussed earlier.

The incorporation of positively charged polymer, such as chitosan, into formulation proved to be an effective permeation enhancer across the buccal mucosa (Table 3). Chitosan, an amine-based polymer with a pKa of 5.5–7, carries a positive charge at a lower pH and exhibits good mucoadhesive properties [121]. N-trimethyl chitosan, exhibiting a positive charge, demonstrated superior enhancement of buccal mucosal permeation for ropinirole hydrochloride when compared to negatively charged sulfobutyl ether-β-cyclodextrin and neutral hydroxypropyl-β-cyclodextrin [98,122]. Due to the mucoadhesive properties of chitosan, the polymer can be an attractive excipient for MBF formulation, promoting retention to buccal mucosa while increasing permeation of hydrophilic or large molecular weight drugs via paracellular pathways. However, it is worth noting that positively charged polymers can cause irritation to the site of administration due to the mechanism of action.

3D printing of mucoadhesive buccal films as an approach to control drug release and dose personalization

Currently, solvent casting is the predominant method for the manufacturing of MBFs. The casting process involves the preparation of a polymeric casting solution, wherein drug, polymer, and additional excipients such as plasticizers are dissolved in a solvent. Once poured into a mold and casted, the buccal films are cut into appropriate dimensions containing the desired dose [123,124]. While solvent casting is a low-cost, straight-forward technique, the process is associated with constraints. Limitations include uneven film thickness, lack of drug uniformity, and the necessity for reduced viscosity to facilitate pouring and casting of the solution, restricting the achievable polymer concentration of films [14,123].

Three-dimensional (3D) printing, also known as additive manufacturing, has become a transformative technology of the twenty-first century. Initially patented by Charles Hull in 1986, 3D printing has since gained widespread application across diverse industries including pharmaceuticals and healthcare [125]. In the pharmaceutical industry, 3D printing reached a significant milestone in 2015 when the U.S. Food and Drug Administration (FDA) approved *Spritam®*, the first and only 3D-printed drug product to date [126,127]. This approval sparked considerable interest among global pharmaceutical manufacturers, due to its potential to redefine drug delivery. By 2015, the global market for 3D printing technologies had reached $5.165 billion and the market is projected to expand further, with an estimated value of $3.692 billion by 2026, growing at a compound annual growth rate (CAGR) of 18.2% [125,127]. This growth underscores the increasing adoption of 3D printing, highlighting its potential to revolutionize the field.

Three-dimensional printing has been recently utilized in the manufacture of oromucosal drug delivery systems, including buccal films [8,128]. Leveraging 3D printing technologies such as stereolithography, powder-based printing, selective sintering, fused filament fabrication, and extrusion-based methods, enables the utilization of a more diverse array of materials – ranging from resins, powders, thermoplastic filaments, and hydrogels possessing wide range of viscosities [129–132].

By harnessing computer-aided design (CAD) software, 3D printing enables the manufacturing of uniform buccal films with intricate and unique complex geometries that are unattainable through conventional drug manufacturing techniques such as solvent casting [133,134].

Implementing 3D printing for manufacturing MBFs enables customization of infill patterns, density, and geometric properties. This customization tailors the film's characteristics and performance to individual needs and is particularly advantageous for geriatric patients whose therapeutic needs vary with age [135]. The individualized approach to medicine relies on clinical data, genetic profiles, and overall health status, to enhance therapeutic outcomes while minimizing side effects [136]. Furthermore, 3D printing has potential to facilitate the manufacture of multilayer combination therapy (co-therapy) MBFs to simplify drug administration, which is especially beneficial for geriatric patients managing comorbidities.

The impact of infill pattern and density on drug release personalization

Infill patterns refer to the internal structure of a 3D printed dosage form, and this influences the physiochemical properties of the buccal film, including mechanical strength and drug release [137,138]. Infill patterns can be exploited to create rectilinear, cubic, and hexagonal pore structures within a MBF to alter and optimize surface area to volume ratios, mediating drug release profiles [137]. A study explored the impact of infill patterns (Figure 1) on the release of estradiol from 3D printed MBFs; the findings revealed rectangular, and honeycomb (hexagonal) infill patterns facilitated faster drug release compared to the 'plain' 100% infill [133]. By modifying the infill geometries and therefore adjusting the available surface area of the buccal film, it becomes possible to optimize drug release kinetics [139].

Moreover, adjustments in infill density, representing the volume of material utilized to occupy the internal layers, can be made. Increasing the infill density of a buccal film increases mechanical strength of the dosage form, however, this can influence drug release [138]. Research has investigated the use of semi-solid extrusion 3D printing to manipulate infill densities and evaluate the effect on drug release [140]. The study examined the effects of 10%, 20%, and 40% infill densities and identified that a 10% infill density led to wider pattern spacing and greater rate of drug dissolution. Therefore, reducing the infill density of a 3D printed buccal film can facilitate a faster drug release rate. However, this reduction of infill density also corresponded to a decrease in mechanical strength of the films [140]. Although greater infill densities improve the mechanical strength of the buccal film, literature notes that drug release rates are proportional to surface area to volume ratios [133,141].

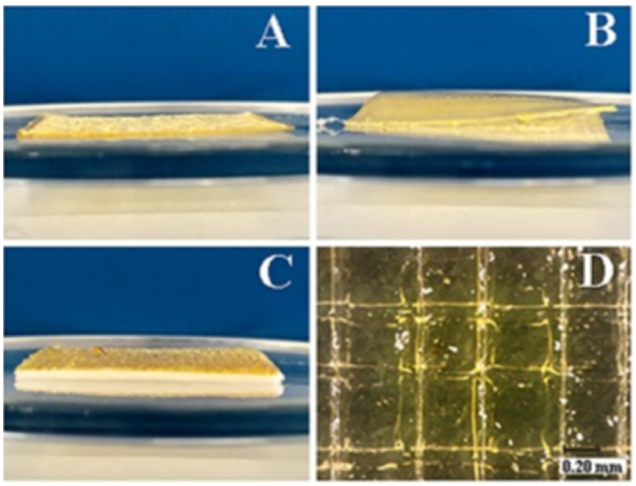

Figure 2. Representative photos of 3D printed films in the absence (A) and presence of ethyl cellulose (B) or wafer (C) backing layers. (D) Optical micrograph of 0C-X formulations (without chitosan, without backing layer) [8], with permission from *European Journal of Pharmaceutics and Biopharmaceutics*.

The level of customization afforded by 3D printed buccal films enables individualized medicine that is patient focused. The flexible infill pattern and density options facilitate the customization and tailoring of drug release profiles based on geriatric patients' therapeutic needs [140]. For instance, where these patients require smaller doses over prolonged periods of time, the surface area to volume ratio can be optimized to facilitate a more sustained release formulation.

The impact of geometry on dose personalization and drug release

Flexible dose adjustments are crucial for meeting the unique needs of geriatric patients due to the age-related physiological changes including renal impairment and liver mass reduction and their effect on drug absorption, metabolism, distribution, and elimination [142,143]. With aging, lean muscle mass and water content decrease, while total body fat proportion increases, significantly affecting how many drugs are distributed throughout the body [143]. These age-related changes to the body are especially important when considering delivery of lipophilic drugs, such as opioids, benzodiazepines, and antipsychotics, as these drugs will have a larger volume of distribution in geriatric patients [142,143]. Therefore, without appropriate dose adjustments patients are at risk of adverse events and overdose caused by prolonged elimination half-life and drug accumulation.

The use of 3D printing to adjust the geometry of buccal films enables further patient-focused customizations by adjusting thickness and size of film to alter the dose [144]. The geometry of a mucoadhesive films can be tailored to individual needs, such as altering catechol-loaded mucoadhesive films based on mouth ulcer size [145]. There has been little research conducted on the effect of different geometries, created by 3D printing, on the rate of drug release in buccal films. The study conducted by Abdella et al. [133] identified that shorter 3D printed buccal film thickness facilitated greater drug release due to greater surface area to volume ratios. Similar findings were also highlighted in other literature which explored the use of 3D printing to alter tablet geometries and the effects on drug release [146,147]. Tailoring drug release profiles based on geriatric patients' individual physiological needs possesses the potential to revolutionize healthcare by preventing drug accumulation and associated toxicity, reducing the occurrence of adverse events in this population. However, *in vivo* studies and clinical trials are required to evidence whether tailoring drug release profiles can minimize adverse events for geriatric patients.

Using 3D printing, the geometry can be adjusted to increase contact surface area between buccal film and the buccal mucosa, optimizing buccal drug delivery. Expanding the surface area of mucoadhesive polymer buccal films facilitates increased interaction between the dosage form and buccal mucosa. A larger contact area enables greater interaction between polymer and mucin chains, enhancing mucoadhesion [148,149]. Utilizing 3D printing allows for the precise alteration of the surface area, facilitating optimal mucoadhesion [142,144,145].

3D printing of multi-layer combination therapy mucoadhesive buccal films

A high pill burden (prescribed >5 tablets or capsules a day) is a prevalent challenge among geriatric patients due to comorbidity and polypharmacy [150,151]. Over 40% of geriatric adults experience polypharmacy, increasing the risk of a high pill burden [152,153]. A high pill burden is especially challenging for dysphagic geriatric patents and can impede compliance in this population [154]. Multilayer buccal films containing multiple drugs, known as fixed dose combination therapy (FDCT), addresses this issue. The FDCT concept, proven successful in forms like the polypill for cardiovascular treatment, improves overall compliance as patients favored the polypill over multiple oral dosage forms [155–157].

Recent studies on FDCT MBFs show promise by combining complimentary drugs with the aim of simplifying treatment of oromucosal inflammatory conditions. The studies designed MBFs intended for the co-delivery of a fast-acting local anesthetic (lidocaine) and a controlled-release non-steroidal anti-inflammatory drug (NSAID) [158,159]. The rapid release lidocaine is desirable for this application because a prompt local anesthetic effect is ideal, while the relatively slower delivery of NSAID ensures optimal anti-inflammatory effect.

Eleftheriadis et al. implement hot melt extrusion (HME) 3D printing to fabricate lidocaine/ketoprofen FDCT MBFs which involves the systematic deposition of material in a layer-by-layer fashion to create a complex multi-layer film [8,159]. Eleftheriadis et al. also utilize fused deposition modeling (FDM) 3D printing to manufacture multilayer films, comprised of a drug layer and additional backing layer (Figure 2). Through the layering approach, 3D printing enables the fabrication of multilayer buccal films featuring diverse functionalities, including impermeable backing layers to facilitate unilateral drug release, drug-loaded reservoirs for controlled and sustained drug delivery and additional mucoadhesive layers to enhance adherence to the buccal mucosa [8,160]. However, there is an opportunity to further develop FDCT multilayer MBFs by altering the design of these layers. These layers can offer versatility in composition, infill patterns and infill densities, allowing for customization to optimize drug delivery [133]. It is worth noting that 3D printing technologies utilizing HME require high processing temperatures (150–230 °C) to extrude drug loaded polymer filaments [161]. The elevated temperatures pose a risk of thermal degradation of the drug, compromising the stability and therapeutic potential of the formulation.

Alternatively, Alves et al. [158] utilizes solvent-casting in the manufacture of multi-layer MBFs, dispensing one layer onto another. Solvent casting typically involves casting thick layers, followed by prolonged drying periods which poses a risk of irregular drug and excipient distribution within the film [162,163]. By integrating 3D printing technology, an in-process drying step can be incorporated in the manufacture of multi-layer buccal films. Simultaneous printing and drying of thin layers mitigate the risk of irregular distribution and facilitates the manufacture of uniform films [164].

Utilizing 3D printing in the manufacture of FDCT multilayer MBFs is especially beneficial for geriatric patients due to their challenges regarding comorbidities and high pill burdens [150,151]. FDCT benefits geriatric patients by simplifying drug administration, replacing multiple oral dosage forms with a single MBF, to improve compliance. By utilizing 3D printing techniques, a tailored MBF can be developed and designed for co-therapy, offering flexible drug doses. This approach reduces pill burden, improves compliance in geriatric patients and encourages individualized drug therapy.

The future 3D printing in buccal film manufacturing

The flexibility afforded by 3D printing enables precise dosage adjustments tailored to individual therapeutic needs, offering a level of customization unattainable with mass-produced buccal films. The ability to 3D-print tailored buccal films has the potential to revolutionize healthcare, particularly within pharmacy and hospital settings [165]. Healthcare practitioners can prepare patient-specific doses using optimized formulations readily available off the shelf [10,166,167].

However, regulatory challenges present a notable barrier to the implementation of 3D printing in healthcare settings. Although the specific regulatory framework for these devices remains unclear, 3D printed buccal films must adhere to the quality, safety, and performance standards established by regulatory bodies [165]. In December 2017, the FDA issued guidance on additive manufacturing for medical devices, outlining regulatory insights, current agency perspectives, and key chemistry, manufacturing, and control (CMC) requirements for approving 3D-printed drugs and devices [125]. The document does not address quality control requirements, printer specifications, or in-process and finished product testing parameters needed to ensure product quality consistency. This is likely due to the wide variety of printers available, each with differing technologies, software, hardware, printing speeds, and quality. Such variability impacts dosage form consistency. To address this, regulatory agencies must deepen their understanding of these technologies and processes, fostering collaboration among researchers, manufacturers, and regulators, to implement thorough regulatory governance and implementation of in-process quality assurance testing.

Furthermore, the successful implementation of 3D printed buccal films depends on the skills and knowledge of the healthcare professionals, particularly pharmacists, as the potential main users [168]. However, the approval of the first 3D printed dosage form, SPRITAM, using ZipDose technology, highlights the potentials of this technology [69].

Conclusion

Literature has identified key age-related challenges to MBF drug delivery. However, by incorporating additional excipients into the formulation, such as permeation enhancers, MBF drug delivery can be optimized, minimizing the effect of age-related biological changes to the oral cavity. Despite these advancements, notable gaps in the understanding remain, including a thorough comprehension of buccal mucosa changes in geriatric populations. Mucoadhesive buccal films have some potential as a therapy for geriatric patients, addressing to the challenges of high pill burden and low compliance. Utilizing 3D printing techniques, FDCT MBFs could simplify geriatric therapy via individualized and tailored co-therapy. However, furthermore clinical studies focusing on the performance and acceptability of MBFs in geriatric populations is required for an extensive insight into the appropriateness of buccal film drug delivery for these patients.

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