Int. j. adv. multidisc. res. stud. 2024; 4(1):630-641

Received: 07-12-2023
Accepted: 17-01-2024

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Therapeutic Potential of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers for Buccal Delivery of Drugs

Melike Üner
Department of Pharmaceutical Technology, Faculty of Pharmacy, Istanbul University, Beyazit, Fatih 34116 Istanbul, Turkiye

Corresponding Author: **Melike Üner**

Abstract
Buccal drug delivery or drug administration to the mouth cavity present several advantages over traditional oral drug delivery. They offer rapid onset of action and enhanced bioavailability of drugs compared to simple oral delivery. The rapid systemic drug action begins avoiding first-pass liver metabolism via the buccal and sublingual route. Scientists focus on the design of microparticulate and colloidal delivery systems to prolong effect and increase bioavailability of actives by retaining them in the buccal mucosa. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC), the second generation of SLN, have also been studying for this purpose-buccal drug delivery and application to the mouth cavity in the last years. These sophisticated colloidal drug delivery systems can combine their own excellent properties and advantages of buccal drug delivery for treatment of several diseases. In this chapter, advantages of SLN and NLC, and new approaches for topical and systemic buccal application of drugs are reviewed.

Keywords: Buccal Delivery, Colloidal Drug Delivery Systems, Mouth Cavity, Nanostructured Lipid Carriers, Solid Lipid Nanoparticles

1. Introduction

Buccal dosage forms are often applied to the palate, the mucosal area in the cheek, or the area between the gingiva and the lip for systemic and local delivery of drugs [1-6]. Various natural, semi-synthetic or synthetic polymers are used to achieve mucoadhesion in these dosage forms [7]. These polymers interact with the mucin layer in the glycoprotein structure of the epithelial tissues, providing adhesion and allowing the dosage form to maintain its integrity in that region. With the aim of systemic delivery, it is purposed to eliminate the liver first pass effect by changing the administration route of drugs and to increase their effectiveness in treatment by improving their bioavailability with their controlled release. Here, buccal administration can offer a better alternative to the traditional oral treatment of many drugs. The advantages of buccal drug delivery systems over conventional dosage forms and the need for their preparation can be listed as follows [8-12].

- The buccal mucosa is an effective absorption site for the systemic effects of drugs due to its rich capillary vascular network.
- The buccal mucosa is more permeable than the skin, which is the most preferred body area for topical application.
- Onset of action for buccal dosage forms is within minutes, similar to intramuscular and subcutenous injections. When a buccal dosage form is administered once, the drug passes directly into the blood stream from absorbing tissues, but the onset of drug action will be delayed after oral administration, which is the most preferred route today. Traditional oral administration takes a while for the drug to reach the absorption site in the gastrointestinal tract and then to be absorbed.
- Drug molecules that directly enter the systemic circulation do not undergo the first pass effect. Thus, the drug is prevented from being metabolized in the liver immediately. Whereas, the drug enters the hepatoenteric bloodstream after oral administration.
- In cases where both rapid action and controlled release are desired, the oral mucosa can be preferred as the application site due to the differences in its structure.
- The buccal mucosa has low enzyme activity compared to the gastrointestinal tract. Thus, drug degradation is lower.
- The high bioavailability of the buccally administered drug allows the application dose to be reduced. Thus, the possibility of the occurrence of side effects of the drug is minimized.

- Local or systemic effect can be achieved by differentiating the geometry and design of the dosage form.
- Prolonged drug delivery can be achieved by prolonging the residence time of the dosage form with the selection of the right bioadhesive polymer.
- Buccal dosage forms are produced with cost-effective manufacturing techniques like other conventional dosage forms.
- Buccal administration is not invasive. Patient compliance is better in buccal application compared to nasal, vaginal and rectal route. Pain is not felt during the application. It can be easily applied to inpatients and unconscious patients.
- In the case of emergency or if deemed necessary, drug administration can be easily discontinued.
- Solid buccal dosage forms such as tablets and patches can be monitored visually and the dosage form is easily withdrawn to interrupt dosing when necessary.

Besides its advantages, buccal drug administration has some disadvantages as listed below [8-12].

- It is difficult to apply drugs that have stability problems at buccal pH, cause irritation, and have bad taste and smell.
- The buccal mucosa has a small surface area compared to the gastrointestinal, nasal, rectal and vaginal mucosa.
- Solid buccal dosage forms should be small in size so that they can remain in the application area and do not disturb the patient. Therefore, the dose of active substance should be at most 50 mg. It is not suitable for every active ingredient.
- The continuation of saliva production causes the drug concentration to decrease in the absorption region and some drug to be swallowed, then drug absorption decreases.
- There is a risk of the patient swallowing the dosage form while eating, drinking and speaking.
- Too much saliva production can cause rapid swelling of the polymer in bioadhesive systems and rapid disintegration of the dosage form.
- In patients with very low saliva production, adequate polymer hydration may not be provided.

Various types of traditional dosage forms including tablets, gels, films and aerosols were formulated for drug administration through the oral cavity by scientists and pharmaceutical companies [13]. Oral mucosa is also a very suitable application site for multiparticular drug carriers to obtain local and systemic effects of actives [14, 15]. Multiparticulate drug delivery systems have also recently been demonstrated to improve penetration and tissue distribution of actives. Moreover, colloidal drug delivery systems can be good alternatives for rapid drug delivery as well as controlled drug delivery via the buccal route [16, 17]. Mucoadhesive particles can prolonge the residence time of the drug at the absorption area and, then deliver the drug to mucous membranes. Thus, sustained drug delivery can be provided. On the other hand, particles can be promoted to directly reach the underlying epithelium by penetrating through the mucus gel layer. In recent studies, new approaches are presented for the preparation of more sophisticated mucoadhesive systems with the design of particles with both mucoadhesive and mucopenetrating properties [13, 18, 19].

Since the early 1990s, a great progress has been made in solid lipid nanotechnology in the treatment of many diseases with different routes of administration. The parameters that specify the physicochemical properties of SLN and NLC and the factors affecting their stability have been extensively studied by different research groups [20-22]. Formulation requirements for their targeting and drug delivery at the cellular level have also been investigated [23, 24]. SLN and NLC have been qualified as sophisticated delivery systems designed for controlled drug release and targeting of drugs. These systems have been investigated primarily for transdermal [25] and parenteral use [26]. They can also be applied by peroral [27], ophthalmic [28], pulmonary [29], nasal [30], buccal [15], vaginal [31] and rectal [32] routes in systemic and topical drug therapy. There are limited number of studies on administration of SLN and NLC to the mouth cavity to obtain systemic and local action of actives. In this review, advances in the development of SLN and NLC for buccal delivery was overeviewed. A special focus on formulation composition of SLN and NLC, dosage forms in what they were incorporated, outcomes of the studies and are presented.

2. Oral cavity and penetration pathways of actives

Surface area of the oral cavity varies between about 135 cm^2 and 215 cm^2 from 9 years old children to adults depending on several factors like gender, age and anatomical differences [33, 34]. The mucosa lining the oral cavity can be categorized into three different types according to their structural features and functions,

- Masticatory mucosa covering the gum and hard palate.
- Lining mucosa covering the lips, fornix, base of the oral cavity, lower part of tongue, buccal mucosa and the soft palate.
- Specialized mucosa covering the dorsum of the tongue.

The buccal mucosa is structurally composed of two layers [35],

- Stratified squamous epithelium (approximately 40-50 cell rows thick),
- Lamina propria connected to the submucosal layer (Fig 1).

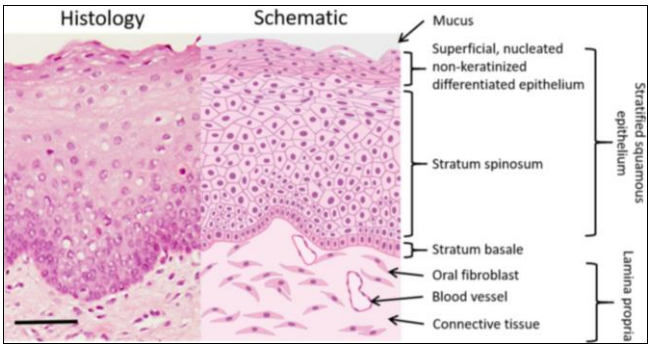

Fig 1: Histological and schematic of buccal mucosa image (by Prof. Keith Hunter, Unit of Oral Pathology, University of Sheffield) (Scale bar = 100 µm) [35]

The oral cavity mucosa also differs in thickness and blood flow depend on the region. The buccal mucosa is 500-800 µm thick, hard and soft palates, floor of the mouth, ventral tongue, and gums are 100-200 µm thick. It contains keratinized and non- keratinized tissues varying in the composition [36] (Table 1).

Table 1: Regional variation in the composition of the mouth cavity mucosa

Tissue	Structure	Thickness of the epithelial layer (µm)	Blood flow (mL/min/cm^2)
Buccal	Non-keratinized contain only small amounts of ceramide.	500-800	2.40
Sublingual		100-200	0.97
Gingival	Keratinized similar to the epidermis contain neutral lipids like ceramides and acylceramides which are relatively impermeable to water.	200	1.47
Palatal		250	0.89

The cheek pocket and sublingual mucosa are the most preferred areas for drug administration in the oral cavity. The permeability of the buccal mucosa is 4-4000 times higher than that of the epidermis layer of the skin and less than that of the intestinal mucosa. On the other hand, absorption of drugs through the sublingual mucosa is 3-10 times greater than the oral mucosa [37]. Actives penetrate through the buccal mucosa by paracellular and transcellular pathways depending on their physicochemical properties (Fig 2) [11, 38].

- Paracellular pathway: It is the passage of the drug through the intercellular spaces between epithelial cells. Due to the hydrophilic nature of the intercellular space, only hydrophilic active substances with a molecular weight of less than 500 Da pass through. The paracellular pathway is also a barrier for lipophilic drugs with low water solubility.
- Transcellular pathway: The transcellular pathway is the passage of active substance through the epithelial cell membrane with polar and lipid content. Epithelial cells are lipophilic in character. Passage of lipophilic drugs with low molecular weight occurs by passive diffusion. Lipophilic active substances pass through the cells and diffuse into the lower layers. The transcellular pathway creates a barrier for water-soluble hydrophilic substances to be overcome. Drug transfer from the intracellular part where the cytoplasm is located is fast and easy, and the cell membrane shows the main barrier feature during diffusion. The total surface area in the transcellular transition is higher than in the paracellular transition. In addition, the path required for the drug to pass through the oral mucosa is much less compared to the paracellular passage. For these reasons, lipophilic substances diffuse more rapidly through the transcellular route.

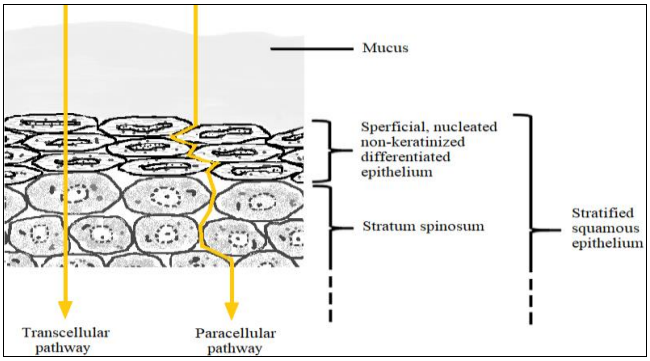

Fig 2: Transfer of active substances through the buccal mucosa by transcellular and paracellular routes (Author's illustration)

Mucoadhesion process of a dosage form has a complicated physicochemical mechanism [39]. The first step is wetting or swelling phenomenon, in other words, diffusion and interference of polymer chains into the mucus layer. An affinitive contact occurs between the bioadhesive dosage form and the buccal epithelium membrane. Following the interpenetration step, chemical or physical bonds (ionic, covalent, hydrogen, hydrophobic bonds and Van der Waals forces) are formed between the interfering polymer chains and the mucin chains.

Factors affecting bioadhesion are drug and polymer-related factors, and environmental and physiological factors. Considering drug-related factors, penetration of drugs through the buccal mucosa depends primarily on the size of the molecule, how lipophilic it is, and its ionization [40, 41]. Molecules smaller than 100 Da can penetrate the buccal mucosa rapidly by diffusion. As the molecular size increases, the permeability of hydrophilic substances decreases. The ionization state of the drug in the oral cavity is an important parameter in the transcellular diffusion [42]. When weakly acidic or weakly basic drugs with pKa values close to 7 are applied to the oral cavity, they are largely non-ionized. Drugs in the non-ionized state have more lipophilic properties than their ionized state. Non-ionized drugs are permeated by the transcellular pathway [11].

There are many environmental and physiological factors affecting bioadhesion. Saliva flow rate and mucin cycle, pH, contact time, eating and drinking are among these factors.

3. Potential of SLN and NLC in the mouth cavity and buccal drug delivery

Unique properties of SLN and NLC, and their advantages over traditional dosage forms and several colloidal drug delivery systems have been reported for years [43-45]. They have a great potential in systemic and topical drug delivery such as intravenous and dermal. They can also be advantageous in the effective treatment of many diseases with buccal delivery. The advantages of SLN and NCL via buccal delivery can be listed as follows:

- They are suitable systems for both soluble and insoluble drugs. They are colloidal drug delivery systems with the highest drug loading capacity.
- They are physically and chemically stable systems. They protect drugs with poor chemical stability by avoiding atmospheric oxygene and light.
- They protect active substances that have stability problems in body fluids and physiological environment such as buccal pH e.t.c.
- They are biocompatible and safe carriers since they are composed of short- and middle-length chain triglycerides and waxes which have the GRAS status (Generally Recognized As Safe) (CFR - Code of Federal Regulations Title 21 - FDA). They can also be produced using less amount of surfactant and avoiding the use of organic solvents compared to other colloidal drug delivery systems.
- There are cost-effective and reproducible large-scale production methods (high-pressure homogenization, coflowing microchannel and supercritical fluid methods) to obtain SLN and NLC dispersions with rich nanoparticle content. In their manufacture, 30% lipid can be stabilized by addition of surfactants up to 5%.
- They are produced with narrow homogeneous particle size distribution. Depending on the particle size of the

SLN and NLC, the drug can be provided to act topically in the oral cavity, or to display systemic effects by passing through the mucosa.
- They protect the buccal mucosa from actives that cause irritation in gastrointestinal tract, and mouth cavity.
- They mask bad taste and smell of actives to be applied via the buccal route.
- They promote the bioavailability of actives by modifying their release profiles. SLN and NLC also improve tissue distribution of actives.
- SLN and NLC can contribute targeting of active agents to the specific organs or cells.
- SLN and NLC are mucoadhesive drug carriers. Their mucoadhesion forces increase with decreasing particle size, which means an increase in surface area.

Mucus layer is a hydrophilic absorption barrier in the mouth cavity [46]. Particle size of nanoparticles contributes to their ability to pass through physiological barriers [47]. Nanoparticles smaller than 150 nm have ability to cross the endothelial barrier [48]. Attachment of bigger nanoparticles to the mucous membrane is essential for drug release from SLN and NLC, and then penetration of the drug through the mouth mucosa, the place of absorption. However, discontinuous endothelium caused by certain pathological conditions with fenestrations as large as 780 nm allows bigger nanoparticles to cross barriers at the application site [49].

When nanoparticles are introduced in a dosage form, the dosage form containing mucoadhesive polimers must adhere to the mucosa at first. SLN and NLC can be introduced in liquid, semi-solid and solid mucoadhesive dosage forms in their dispersion or lyophilized forms. Indeed, mucoadhesion is a complex process that occurs with wetting, adsorption and interpenetration of polymer chains. Type of the vesicle in which nanoparticles incorporated is crucial to obtain especially the systemic activity of the drug. In order for the drug to be absorbed by the mucosa, it must be released from nanoparticles and then from polymer network. Therefore, the dosage form must remain on the mucosa for a sufficient time. Theories conduct the mucoadhesion of polymers are discussed in detail in the literature - electronic theory, wetting theory, adsorption theory, diffusion theory, mechanical theory and cohesive theory [39, 50].

Bioadhesive polymers used in dosage forms containing SLN and NLC

Different polymers show different mucoadhesive properties depending on their physical and chemical strengths (Table 2).

Table 2: Some of the most commonly used bioadhesive polymers, their electrical charges and types of chemical bonding

Electrical Charge	Polymers	Type of bonds for mucoadhesion	References
Anionic	Acacia gum	Hydrogen bonds	[51]
	Sodium alginate	Hydrogen bonds	[52]
	Carbomers	- Hydrogen bonds - Hydrophobic interactions controlled by pH and ionic composition - Van der Waals bonds - Thermosensitive	[53, 54]
	Carrageenan	Hydrogen bonds	[51]
	Gellan gum	Hydrogen bonds	[55]
	Lectins	Cytoadhesion (cell-specific bioadhesion)	[56]
	Pectin	Hydrogen bonds	[57]
	Polycarbophil	- Hydrogen bonds - Hydrophobic interactions controlled by pH and ionic composition - Van der Waals bonds - Thermosensitive	[58]
	Sodium hyaluronate	Hydrogen bonds	[59,60]
	Tamarind gum	Hydrogen bonds	[51]
	Sodium carboxymethyl cellulose (Na-CMC)	Hydrogen bonds	[61]
	Xanthan gum	Hydrogen bonds	[62]
Cationic	Chitosan	- Electrostastic interaction - Hydrogen bonds	[10]
	Gelatin	Hydrogen bonds	[63]
Nonionic	Hydroxypropyl methylcellulose (HPMC)	Hydrogen bonds	[54]
	Hydroxypropyl cellulose (HPC)	Hydrogen bonds	[64]
	Guar gum	Hydrogen bonds	[65]
	Polyethylene glycol (PEG) and polyethylene oxide (PEO)	Hydrogen bonds	[66]
	Polyvinylpyrollidone (PVP)	Hydrogen bonds	[66]
	Thiomers	- Disulfide bonds - Covalent bonds	[67,68]

Understanding the various mechanisms that govern the binding of polymers to glycoproteins on epithelial surfaces and their structure-activity relationships is important in the design of buccal dosage forms. Four possible interactions between mucoadhesive polymers and glycoproteins have been reported [69].

- Covalent attachment,
- Electrostatic interaction,
- Hydrogen bonding and
- Hydrophobic interactions.

Mechanisms other than covalent bonding demand maximum contact between polymer and mucin for desired adhesion. Matching of charge groups between the polymer and the mucus is required for electrostatic interaction. If polyelectrolyte polymers are used, their charged groups control the degree of hydration in the polymer and the mucous networks. As an interdiffusion process develops between the network of the swollen polymer and the mucus, there is an increase in contact surface for hydrogen bonding and/or electrostatic interaction. Various characteristics of polymers affect their mucoadhesive properties including functional group, concentration, molecular weight charge, chain length, degree of hydration, degree of cross-linking and flexibility. They are generally desired to have the following properties [7, 70].

- They should have sufficient amount of functional groups such as OH, COOH, NH_2 and SO_4H to form strong bioadhesive bonds with mucin.
- They should be able to adhere to the mucosa easily and quickly.
- Their structure should remain intact on the surface on which they are applied throughout the controlled release.
- They should swell easily in the area where they are applied.
- They must have high molecular weight. As the molecular weight increases (MW > 100 000), the bioadhesion becomes stronger.
- Their chain flexibility must be high. As the flexibility of the polymer chains increases, the diffusion of the biological fluid increases and the mucoadhesion improves.
- They must have the surface tension that may induce spreading into mucous layer.
- They should not be irritant.
- They should not have an undesirable taste and smell.

Aqueous nanoparticle dispersions

SLN and NLC can be applied with an applicator or by spraying into the mouth cavity as liquid or viscous dispersions (Tables 3 and 4). Thus, nanoparticles themselves come into close contact with mucin glycoproteins on the buccal epithelium, resulting in mucoadhesion. More precisely, due to the submicron particle size of the nanoparticles, direct contact with the mucous membrane in the area where they are applied (i.e. not in a dosage form) ensures that the effect of the drug begins rapidly and continues for a long time. Studies have also shown that SLN and NLC dispersions allow rapid and effective treatment, especially in the local treatment of intraoral infections, wounds and lesions. They can be used for daily mouth care of healty people or patients under nursing care. In a study their high potential was reported for the treatment of discontinuous epithelium/endothelium layers and deeper tissues of the mucosa due to their small particle size [47]. The discontinuous epithelium of the damaged site display with large fenestrations up to 780 nm [48, 49].

Hydrogels

Hydrogels are hydrophilic, three-dimensional polymeric lattice molecules absorbing biological fluids and more than 20% water by weight [97]. Hydrogels can be classified as neutral or ionic, depending on the ionization behaviours of the polymers (Table 2). In other words, whether they are anionic, cationic or neutral in nature determines the properties of hydrogels. The ionic interaction and repulsion between the charged polymer chains and free ions play an important role in the swelling of ionic hydrogels. In this case, drug or protein transfer at ionic gels is markedly different than neutral gels. The biological activity is maintained until the drug release from the hydrogel is completed. A tight structure is seen in hydrogels with high cross-linking. The drug release depends on the degree of swelling and cross-linking of the hydrogel. In this case of high-cross linking, the limited movement of the chains prevents the hydrogel from swelling. However, in hydrogels with low cross-linking, the chains can move freely and swelling is facilitated.

Hydrogels may also exhibit swelling behavior depending on the external environment. Environmentally-sensitive hydrogels display remarkable changes in their swelling behavior, network structure, permeability or mechanical strength in response to changes in the pH or ionic strength of the surrounding fluid, or temperature. They change from the sol form to the gel form under the physiological conditions of the body.

SLN and NLC in hydrogels can be applied by using an applicator to the buccal cavity. In most cases, they are lyophilized before incorporation in hydrogels (Tables 3 and 4).

Thin films

Buccal films have been formulated as potential dosage forms for application of SLN and NLC to the buccal mucosa by various research groups (Tables 3 and 4). There are different types of films composed of polymer, sweetener and/or aromatic substances besides the drug. They are designed in a single or double layer, thin and flexible structure for immediate or prolonged drug delivery. They may be soluble (orodispersible) or insoluble in saliva [98]. Despite the ease of application, buccal films have disadvantages such as changing the location of the during eating and drinking or being swallowed unintentionally.

Patches

Buccal patches consist of backing layer maintaing the geometry of the patch and drug-loaded reservoir adhering to the mucosal surface. While the backing layer prevents the release of the drug from the outer surface of the patch, the drug release from the reservoir layer occurs from the surface where the patch adheres to the mucosa [75]. The reservoir layer of patches is composed of the active agent, polymer and plasticiser similar to buccal films. Polymer chains come close contact with the mucin layer of the mucosa and mucoadhesion occurs. They should be thin, flexible and 1-3 cm^2 to be comfortable for patients. Buccal patches have been demonstrated to be good canditates for application of

SLN and NLC in the mouth cavity (Tables 3 and 4).

Tablets

Buccal tablets are flat and thin solid dosage forms with a diameter of 5-8 mm, which are used in the systemic treatment of various diseases or in the local treatment of oral wounds and infections [99, 100]. They can be applied to the palate or buccal mucosa, or to the area between the gingiva and the lip. Buccal tablets are usually produced by direct compression of powder blends or multiparticulate drug delivery systems [10, 101]. Various natural, semi-synthetic or synthetic polymers are used in buccal tablets to achieve mucoadhesion (Table 2). These polymers interact with the mucin layer in the glycoprotein structure of epithelial tissues, providing adhesion and allowing the tablet to maintain its integrity in that region [7, 12]. Drug release from buccal tablets can occur unilaterally or bilaterally, depending on the desired effect. One surface of the tablets is usually coated with ethyl cellulose in order to achieve unilateral release [55].

SLN and NLC in the dry powder form are incorporated in powder blends before tabletting (Tables 3 and 4). SLN and NLC powder can be obtained by removing the aqueous continuous phase of their dispersions by spray-drying or lyophilization processes [80, 102]. SLN and NLC can also be loaded into new generation multiparticle drug delivery systems such as microsponges, which various research groups have focused on in recent years [85]. Then, nanoparticle loaded sponges are incorporated in a mucoadhesive powder blend, and compressed as tablets for buccal delivery. However, NLC and SLN dispersions can also be added directly to the tablets prepared by the wet granulation method at the first wetting process of the powder mixture. In this case, nanoparticle dispersion is used as wetting agent or granulation fluid in the production process of pellets or granules, and then bulk products can be compressed into tablets [43, 103].

A buccal tablet must be sufficiently swollen to ensure uniform and controlled release of the drug and subsequent drug absorption through the mucous membrane. It is related to the correct selection of polymers that form an adequate swelling tablet. Thus, weak bonds are formed and mucoadhesion occurs [104]. Good swelling of tablets can be attributed to the ability of polymers to absorb water continuously and addition of high hydrophilic polymers increasing water uptake capacity such as PVP [105].

Table 3: Studies on design of SLN formulations for administration into the mouth cavity

Active Agents	Solid Lipids	Surface Active Agents	Production Methods	Dosage Forms	Outcomes	References
Coumarin 6	Lipoid S100	Tween® 80	Solvent injection	HPMC film	A SLN loaded mucoadhesive film formulation with uniformity, mucoadhesiveness and biocompatibility was developed.	[71]
Curcumin	Gelucire® 50/13	Poloxamer® 407	High shear homogenization	Lyophilized CMC sodium, polyvinyl alcohol, gellan gum, HPMC 4000, polycarbophil and chitosan sponges	The polycarbophil sponge was revealed to have the best properties compared to the others and to provide sustained release and constant curcumin concentration in the buccal cavity over 14-15 hours.	[72]
	Gelucire 39/01 Gelucire® 50/13 Compritol 888 ATO Precirol ATO5	Gelucire® 50/13 Poloxamer 407	High shear homogenization	SLN dispersions	Chemical stability of curcumin against degradation was provided. Antimicrobial and antifungal activity could be effectively enhanced by incorporation of curcumin into SLN.	[73]
	Gelucire® 50/13	Poloxamer® 407	High shear homogenization	Gels composed of poloxamer 407 and polycarbophil mixtures at different ratios.	SLN composed of Gelucire 50/13 and PX407 displayed good mucosal uptake to be used for treatment of precancerous oral lesions.	[74]
Diclofenac diethylamine	Precirol® ATO 5 and Geleol™ mixture	Pluronic F 68	Solvent emulsion–evaporation	Transmucosal patch prepared with HPC film	The drug permeated from the patch through porcine buccal mucosa over 24 hours. Significant increase in drug bioavailability was provided to obtain anesthesia and analgesia for dental procedures.	[75]
Cyclosporin A	Compritol 888 ATO	Poloxamer 188 and Tween 80 mixture	Hot high-shear homogenization	Carbopol 974 P NF and HPMC K 100M gels	The bioadhesive gel formulation of SLN increased the rate of mucosal repair significantly. It was decided to be promising candidate for the topical treatment of recurrent aphthous stomatitis.	[76]
Didanosine	Glyceryl tripalmitate	Poloxamer 188	Hot homogenization followed by ultrasonication	Monolayered multipolymeric films	A potential buccal drug delivery system was designed to enhance antiretroviral treatment in human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS)	[77]
Fluconazole	Glyceryl monostearate	Tween® 80	Ultrasonication	Chitosan films	The drug from the the films containing SLN was determined to be more permeable than traditional films	[78]

					for treatment of candidiasis.	
Idarubicin	Emulsifying wax	Brij® 78	Microemulsion	SLN dispersion	Nanoparticle internalization by OSCC (oral squamous cell carcinoma) cells and higher final intracellular levels compared to bolus administration.	[79]
Lornoxicam	Stearic acid	Soy lecithin and Cremophor® RH 40	Hot homogenization followed by ultrasonication	PVP K30 and HPMC K15 tablet	Mucoadhesive buccal tablets containing SLN were developed with enhanced bioavailability, and achieving a controlled release profile to obtain systemic anti-inflammatory effect.	[80]
Metronidazole (antibacterial)	Precirol® ATO 5	Tween® 80	Solvent evaporation and hot homogenization	HEC gel	SLN formulation in gel displayed sustained drug release, optimal permeability, and enhanced antimicrobial activity over 24 hours for managing periodontitis characterized by chronic inflammation of the soft tissue surrounding the teeth.	[81]
Neomycine sulfate	Stearic acid and glycerol monostearate	Soya lecithin and Pluronic® F68	Solvent injection	Kolliphor® P 407 gel	SLN formulation in gel displayed sustained drug release, excellent permeability and increased antibacterial activity for treatment of mucosal wound healing	[82]
Nicotine	Hydrogenated sunflower oil	Polyvinyl alcohol	Hot high pressure homogenization	Pure drug and, stearic acid and Kolliwax® S lipid-drug-conjugates in water and sodium carbonate-sodium bicarbonate buffer at pH 9.0	Higher drug loading capacity with (~50%) lipid-drug-conjugates compared to SLN of the pure drug (~10%).	[83]
Polymyxin B	Lipoid S75®	Pluronic F68®	Hot high pressure homogenization	Not mentioned	The validated UV spectrophotometric assay was demonstrated to be fast and suitable for the quantification of the drug incorporated in SLN.	[84]

Table 4: Studies on design of NLC formulations for administration into the mouth cavity

Active Agents	Solid Lipids/Liquid Lipids	Surface Active Agents	Production Methods	Dosage Forms	Outcomes	References
Celecoxib	Stearic acid/Oleic acid	Poloxamer 188	Solvent evaporation technique	Pluronic F127 and Carbopol 934 in situ gels	The Carbopol 934 containing gel formulation exhibited the best *insitu* gelling properties regarding spreadability, mucoadhesion and permeation. Bioavailability of the drug was improved.	[64]
Curcumin and metronidazole	1-Hexadecanol/Isopropyl palmitate	Tween 20	Homogenization followed by ultrasonication at room temperature and cold.	Tabletted sponges	Tablets were able to release the actives promoting their penetration and permeation through the mucosa for treatment of oral infections and periodontitis.	[85]
		Tween 80 and/or Pluronic F-68	Hot homogenization followed by ultrasonication		Formulations were able to release the actives promoting their penetration and permeation through the mucosa for applying leukocyte and platelet-rich fibrin clot to promote tissue regeneration in dentistry.	[86]
Domperidone	Palmitic acid/Oleic acid	Tween® 80	Hot high pressure homogenization	NLC dispersion	NLC were found to be appropriate carrier systems that facilitate the transport of the poorly soluble drug across buccal and sublingual tissue for preventing vomiting and nausea in chemotherapy treated cancer patients.	[87]
Fluconazole	Stearic acid/Oleic acid	Pluronic F127 and lecithin	Hot homogenization followed by ultrasonication	NLC dispersion	Coating the nanoparticles with chitosan increased their adhesion to buccal mucosa and improved its anti-candidiasis activity.	[88]
Glimepiride	Compritol 934 and soybean phosphatidylcholine/Alm	Gelucire 44/14	Hot homogenization followed by	HPMC films	NLC film displayed sustained release of the drug over 6 hours and ability to transport the drug across the buccal	[89]

	ond oil		ultrasonication		mucosa for treatment of diabetes mellitus	
Ibuprofen	Precirol® ATO 5 / Miglyol® 812	Tween® 80	Hot homogenization followed by ultrasonication/Hot high pressure homogenization	Carbopol1 980 gels Polycarbophil gels	Different production methods presented close particle size in the nanometric size range and desirable physical properties, and efficient ability for the entrapment of the drug. Carbopol® 980 gels exhibited greater residence time on the mucosa.	[90]
Lidocaine-Prilocaine	Cetyl palmitate/Capric, caprylic triglycerides	Pluronic® 68	Hot homogenization followed by ultrasonication	Hybrid nanogels of alginate, chitosan, xanthan gum	The nanohybrid hydrogel of xhantan gum displayed the best characteristics as a biopolymer. It was stable for 6 months. The formulation displayed local anethetic effect for 8 hours.	[91]
	Cetyl palmitate/Capric, caprylic triglycerides	Pluronıc 188	Hot homogenization followed by ultrasonication	Pectin based hybrid nanofilms	Release profile of the drugs was prolonged for approximately 8 hours. Higher drug permeation and longest-lasting anesthesia were observed more than 7 hours and 3 times longer than traditional dosage forms.	[92]
Miconazole	Gelucire® 43/01 / Miglyol® 812	Tween® 80	Hot homogenization followed by ultrasonication	Gelling PFC® gels	Good physical stability, high encapsulation efficiency and controlled drug release were determined. Improved antifungal activity against *Candida albicans* was obtained with 17-fold lower dose of the drug compared to a commercial oral gel formulation.	[93]
	Compritol /Sesame oil	Labrasol	Hot homogenization followed by ultrasonication	NLC dispersion	Increased permeation rate of the drug through the buccal mucosa was significantly higher than a marketed formulation for inhibiting the growth of *Candida albicans*.	[94]
Pranoprofen	Lanette® 18/ Castor oil	Tween® 80	Hot high pressure homogenization	NLC dispersion	The formulation exhibited desirable characteristics. High permeation and high retention of the drug were observed.	[95]
Sage extract	Cutina CP/Sage extract	Lutrol F68	Hot high pressure homogenization	Spray	The formulation exhibited desirable characteristics. Taste of the formulation was found to be perciviable for 6 hours to be used for mouth and throat care in healty people and patients under nursing.	[47]
Triamcinolone acetonide	Spermaceti/Soybean oil	Tween® 80	Hot homogenization followed by ultrasonication	NLC dispersion	The formulation could be an efficient carrier for drug delivery through the buccal mucosa with high penetration depth at 8th hour after application. It can be an efficient alternative for treatment of many dieases including arthritis, oral inflammation and allergies.	[96]

4. Conclusions

SLN and NLC are colloidal drug delivery systems that can be produced on a large scale with versatile methods that have been used in the food industry for years. Their components are low-cost chemicals used in medicine, cosmetics and food. Their therapeutic potential has increased the interest in these systems. SLN and NLC have mucoadhesive property by their nature. Thus, they have been demonstrated to improve buccal absorption and bioavailability of many drugs. They are also promising drug carrier system for topical administration of actives to the mouth cavity. Bioadhesive properties of SLN and NLC allow their residence in the oral cavity and prolonged drug release. Their paracellular transport through the endotellium in the buccal cavity can be achieved by producing them with particle size less than 150 nm. Thus, they may penetrate deeper layer of the mucosa and display reservoir action, or attend systemic circulation. Buccal SLN and NLC have significant potential in topical or systemic treatment of many diseases. They may also contribute to increasing the patient's compliace to treatment in diseases that threaten life and/or negatively affect the quality of patient's life. SLN and NLC are sophisticated systems that can be an effective alternative to treatment with conventional dosage forms and their counter-parts due to their many advantages.

5. References

1. Tang GH, Xu J, Chen RJ, Qian YF, Shen G. Lithium delivery enhances bone growth during midpalatal expansion. J Dent Res. 2011; 90(3):336-340.
2. Bera H, Gaini C, Kumar S, Sarkar S, Boddupalli S, Ippagunta SR. HPMC-based gastroretentive dual working matrices coated with Ca($^{+}$2) ion crosslinked alginate-fenugreek gum gel membrane. Mater Sci Eng C Mater Biol Appl. 2016; 67:170-181.
3. Anita L, Venkatesh DP, Sajeev Kumar B, Kanni P, Ramnarayanan C, Karki R, *et al*. Extraction, purification, and development of sublingual film (slit

films) comprising cockroach allergen for treatment of allergy. Curr Drug Deliv. 2023; 20(6):807-817.
4. Surendranath M, Ramesan RM, Nair P, Parameswaran R. Electrospun mucoadhesive zein/PVP fibroporous membrane for transepithelial delivery of propranolol hydrochloride. Mol Pharm. 2023; 20(1):508-523.
5. Xu M, Chen G, Dong Y, Yang J, Liu Y, Song H, *et al*. Liraglutide-loaded milk exosomes lower blood glucose when given by sublingual route. Chem Med Chem. 2022; 17(10):e202100758.
6. Satheesh Madhav NV, Semwal R, Semwal DK, Semwal RB. Recent trends in oral transmucosal drug delivery systems: An emphasis on the soft palatal route. Expert Opin Drug Deliv. 2012; 9(6):629-647.
7. Laffleur F. Mucoadhesive polymers for buccal drug delivery. Drug Dev Ind Pharm. 2014; 40(5):591-598.
8. Shinkar DM, Dhake AS, Setty CM. Drug delivery from the oral cavity: A focus on mucoadhesive buccal drug delivery systems. PDA J Pharm Sci Technol. 2012; 66(5):466-500.
9. Fonseca-Santos B, Chorilli M. An overview of polymeric dosage forms in buccal drug delivery: State of art, design of formulations and their *in vivo* performance evaluation. Mater Sci Eng C. 2018; 86:129-143.
10. Abruzzo A, Cerchiara T, Bigucci F, Gallucci MC, Luppi B. Mucoadhesive buccal tablets based on chitosan/gelatin microparticles for delivery of propranolol hydrochloride. J Pharm Sci. 2015; 104(12):4365-4372.
11. Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhesive drug delivery-a promising option for orally less efficient drugs. J Control Release. 2006; 114(1):15-40.
12. Salamat-Miller N, Chittchang M, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Deliv Rev. 2005; 57:1666-1691.
13. Esposito D, Conte C, d'Angelo I, Miro A, Ungaro F, Quaglia F. Mucoadhesive zein/beta-cyclodextrin nanoparticles for the buccal delivery of curcumin. Int J Pharm. 2020; 586:119587.
14. Jelvehgari M, Valizadeh H, Jalali Motlagh R, Montazam H. Formulation and physicochemical characterization of buccoadhesive microspheres containing diclofenac sodium. Adv Pharm Bull. 2014; 4(3):295-301.
15. De Caro V, Giannola LI, Di Prima G. Solid and semisolid innovative formulations containing miconazole-loaded solid lipid microparticles to promote drug entrapment into the buccal mucosa. Pharmaceutics. 2021; 13(9):1361.
16. Lim LM, Hadinoto K. High-payload buccal delivery system of amorphous curcumin-chitosan nanoparticle complex in hydroxypropyl methylcellulose and starch films. Int J Mol Sci. 2021; 22(17):9399.
17. Al-Domi D, Bozeya A, Al-Fandi M. Development of an Insulin nano-delivery system through buccal Administration. Curr Drug Deliv. 2022; 19(8):889-901.
18. Inchaurraga L, Martín-Arbella N, Zabaleta V, Quincoces G, Peñuelas I, Irache JM. *In vivo* study of the mucus-permeating properties of PEG-coated nanoparticles following oral administration. Eur J Pharm Biopharm. 2015; 97(Pt A):280-289.
19. Bruschi ML, de Souza Ferreira SB, da Silva JB. Chapter 4 - Mucoadhesive and mucus-penetrating polymers for drug delivery. In: Martins JP, Santos HA. (eds.) Nanotechnology for Oral Drug Delivery: From Concept to Applications. 1st edn. Elsevier, 2020, 77-141.
20. Zimmermann E, Souto EB, Müller RH. Physicochemical investigations on the structure of drug-free and drug-loaded solid lipid nanoparticles (SLN) by means of DSC and ^{1}H NMR. Pharmazie. 2005; 60(7):508-513.
21. Üner M. Preparation, characterization and physico-chemical properties of solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC): Their benefits as colloidal drug carrier systems. Pharmazie. 2006; 61(5):375-386.
22. Andonova V, Peneva P. Characterization methods for solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC). Curr Pharm Des. 2017; 23(43):6630-6642.
23. Tabatt K, Sameti M, Olbrich C, Müller RH, Lehr CM. Effect of cationic lipid and matrix lipid composition on solid lipid nanoparticle-mediated gene transfer. Eur J Pharm Biopharm. 2004; 57(2):155-162.
24. Göppert TM, Müller RH. Adsorption kinetics of plasma proteins on solid lipid nanoparticles for drug targeting. Int J Pharm. 2005; 302(1-2):172-186.
25. Gu Y, Yang M, Tang X, Wang T, Yang D, Zhai G, *et al*. Lipid nanoparticles loading triptolide for transdermal delivery: Mechanisms of penetration enhancement and transport properties. J Nanobiotechnology. 2018; 16(1):68.
26. Wen CJ, Yen TC, Al-Suwayeh SA, Chang HW, Fang JY. *In vivo* real-time fluorescence visualization and brain-targeting mechanisms of lipid nanocarriers with different fatty ester:oil ratios. Nanomedicine (Lond). 2011; 6(9):1545-1559.
27. Yang S, Zhu J, Lu Y, Liang B, Yang C. Body distribution of camptothecin solid lipid nanoparticles after oral administration. Pharm Res. 1999; 16(5):751-757.
28. Üner B, Özdemir S, Yıldırım E, Yaba Ucar A, Taş Ç, Üner M, *et al*. Loteprednol loaded nanoformulations for corneal delivery: Ex-vivo permeation study, ocular safety assessment and stability studies. J Drug Deliv Sci Tech. 2023; 81:104252.
29. Jaafar-Maalej C, Andrieu V, Elaissari A, Fessi H. Beclomethasone-loaded lipidic nanocarriers for pulmonary drug delivery: Preparation, characterization and *in vitro* drug release. J Nanosci Nanotechnol. 2011; 11(3):1841-1851.
30. Costa CP, Cunha S, Moreira JN, Silva R, Gil-Martins E, Silva V, *et al*. Quality by design (QbD) optimization of diazepam-loaded nanostructured lipid carriers (NLC) for nose-to-brain delivery: Toxicological effect of surface charge on human neuronal cells. Int J Pharm. 2021; 607:120933.
31. Sato MR, Oshiro-Junior JA, Rodero CF, Boni FI, Araújo VHS, Bauab TM, *et al*. Photodynamic therapy-mediated hypericin-loaded nanostructured lipid carriers against vulvovaginal candidiasis. J Mycol Med. 2022; 32(4):101296.
32. Huang CH, Hu PY, Wu QY, Xia MY, Zhang WL, Lei ZQ, *et al*. Preparation, *in vitro* and *in vivo* evaluation of thermosensitive in situ gel loaded with ibuprofen-Solid

lipid nanoparticles for rectal delivery. Drug Des Devel Ther. 2022; 16:1407-1431.
33. Collins LMC, Dawes C. The surface area of the adult human mouth and thickness of the salivary film covering the teeth and oral mucosa. J Dent Res. 1987; 66(8):1300-1302.
34. Kerr WJS, Kelly J, Geddes DAM. The areas of various surfaces in the human mouth from nine years to adulthood. J Dent Res. 1991; 70(12):1528-1530.
35. Edmans JG, Clitherow KH, Murdoch C, Hatton PV, Spain SG, Colley HE. Mucoadhesive electrospun fibre-based technologies for oral medicine. Pharmaceutics. 2020; 12(6):504.
36. Harris D, Robinson JR. Drug delivery via the mucous membranes of the oral cavity. J Pharm Sci. 1992; 81(1):1-10.
37. Narang N, Sharma J. Sublingual mucosa as a route for systemic drug delivery. Int J Pharm Pharm Sci. 2011; 3(Suppl 2):18-22.
38. Wanasathop A, Patel PB, Choi HA, Li SK. Permeability of buccal mucosa. Pharmaceutics. 2021; 13(11):1814.
39. Smart JD. Buccal drug delivery. Expert Opin Drug Deliv. 2005; 2(3):507-517.
40. Mashru R, Sutariya V, Sankalia M, Sankalia J. Transbuccal delivery of lamotrigine across porcine buccal mucosa: *In vitro* determination of routes of buccal transport. J Pharm Pharm Sci. 2005; 8(1):54-62.
41. Kokate A, Li X, Jasti B. Effect of drug lipophilicity and ıonization on permeability across the buccal mucosa: A technical note. AAPS PharmSciTech. 2008; 9(2):501-504.
42. Deneer VH, Drese GB, Roemelé PE, Verhoef JC, Lie-A-Huen L, Kingma JH, *et al*. Buccal transport of flecainide and sotalol: Effect of a bile salt and ionization state. Int J Pharm. 2002; 241(1):127-134.
43. Muchow M, Maincent P, Müller RH. Lipid nanoparticles with a solid matrix (SLN®, NLC®, LDC®) for oral drug delivery. Drug Dev Ind Pharm. 2008; 34(12):1394-1405.
44. Silva AC, Amaral MH, Lobo JM, Lopes CM. Lipid nanoparticles for the delivery of biopharmaceuticals. Curr Pharm Biotechnol. 2015; 16(4):291-302.
45. Üner M, Damgali Ş, Özdemir S, Çelik B. Therapeutic potential of drug delivery by means of lipid nanoparticles: Reality or illusion? Curr Pharm Des. 2017; 23(43):6573-6591.
46. Cone RA. Barrier properties of mucus. Adv Drug Deliv Rev. 2009; 61(2):75-85.
47. Üner M, Müller RH. Sage extract entrapped in nanostructured lipid carriers for application into the mouth cavity for oral hygiene. Curr Top Nutraceutical Res. 2012; 10(3-4):193-200.
48. Gaumet M, Vargas A, Gurny R, Delie F. Nanoparticles for drug delivery: The need for precision in reporting particle size parameters. Eur J Pharm Biopharm. 2008; 69(1):1-9.
49. Hobbs SK, Monsky WL, Yuan F, Roberts WG, Griffith L, Torchilin VP, *et al*. Regulation of transport pathways in tumor vessels: Role of tumor type and microenvironment. Proc Natl Acad Sci USA. 1998; 95:4607-4612.
50. Subramanian P. Mucoadhesive delivery system: A smart way to improve bioavailability of nutraceuticals. Foods. 2021; 10(6):1362.
51. Kiniwa R, Miyake M, Kimura S, Itai S, Kondo H, Iwao Y. Development of muco-adhesive orally disintegrating tablets containing tamarind gum-coated tea powders for oral care. Int J Pharm X. 2019; 1:100012.
52. Pamlényi K, Kristó K, Sovány T, Regdon G Jr. Development and evaluation of bioadhesive buccal films based on sodium alginate for allergy therapy. Heliyon. 2022; 8(8):e10364.
53. Asane GS, Nirmal SA, Rasal KB, Naik AA, Mahadik MS, Rao YM. Polymers for mucoadhesive drug delivey system: A current status. Drug Dev Ind Pharm. 2008; 34:1246-1266.
54. Panda B, Subhadarsini R, Mallick S. Biointerfacial phenomena of amlodipine buccomucosal tablets of HPMC matrix system containing polyacrylate polymer/-cyclodextrin: Correlation of swelling and drug delivery performance. Expert Opin Drug Deliv. 2016; 13(5):633-643.
55. Remuñán-López C, Portero A, Vila-Jato JL, Alonso MJ. Design and evaluation of chitosan/ethylcellulose mucoadhesive bilayered devices for buccal drug delivery. J Control Release. 1998; 55(2-3):143-152.
56. Wirth M, Gerhardt K, Wurm C, Gabor F. Lectin-mediated drug delivery: Influence of mucin on cytoadhesion of plant lectins *in vitro*. J Control Release. 2002; 79(1-3):183-191.
57. Laffleur F, Zilio M, Menzel C, Lupo N, Schmutzler M. Design, modification and *in vitro* evaluation of pectin's bucco-adhesiveness. Ther Deliv. 2016; 7(6):369-375.
58. Kraisit P, Limmatvapirat S, Luangtana-Anan M, Sriamornsak P. Buccal administration of mucoadhesive blend films saturated with propranolol loaded nanoparticles. Asian J Pharm Sci. 2018; 13(1):34-43.
59. Walicová V, Gajdziok J, Gajdošová M, Vetchý D. The influence of hyaluronan addition on thickness, weight, uniformity of mass and water content of mucoadhesive films. Ceska Slov Farm. 2016; 65(3):94-98.
60. Park HY, Kweon DK, Kim JK. Molecular weight-dependent hyaluronic acid permeability and tight junction modulation in human buccal TR146 cell monolayers. Int J Biol Macromol. 2023; 227:182-192.
61. Chen J, Duan H, Pan H, Yang X, Pan W. Two types of core/shell fibers based on carboxymethyl chitosan and Sodium carboxymethyl cellulose with self-assembled liposome for buccal delivery of carvedilol across TR146 cell culture and porcine buccal mucosa. Int J Biol Macromol. 2019; 128:700-709.
62. Shiledar RR, Tagalpallewar AA, Kokare CR. Formulation and *in vitro* evaluation of xanthan gum-based bilayered mucoadhesive buccal patches of zolmitriptan. Carbohydr Polym. 2014; 101:1234-1242.
63. Göbel A, da Silva JB, Cook M, Breitkreutz J. Development of buccal film formulations and their mucoadhesive performance in biomimetic models. Int J Pharm. 2021; 610:121233.
64. Reddy Hv R, Bhattacharyya S. *In vitro* evaluation of mucoadhesive in situ nanogel of celecoxib for buccal delivery. Ann Pharm Fr. 2021; 79(4):418-430.
65. Castro PM, Baptista P, Madureira AR, Sarmento B, Pintado ME. Combination of PLGA nanoparticles with mucoadhesive guar-gum films for buccal delivery of antihypertensive peptide. Int J Pharm. 2018; 547(1-2):593-601.
66. Tsibouklis J, Middleton AM, Patel N, Pratten J. Toward

mucoadhesive hydrogel formulations for the management of xerostomia: The physicochemical, biological, and pharmacological considerations. J Biomed Mater Res A. 2013; 101(11):3327-3338.
67. Langoth N, Kalbe J, Bernkop-Schnürch A. Development of buccal drug delivery systems based on a thiolated polymer. Int J Pharm. 2003; 252(1-2):141-148.
68. Laffleur F, Shahnaz G, Islambulchilar Z, Bernkop-Schnürch A. Design and *in vitro* evaluation of a novel polymeric excipient for buccal applications. Future Med Chem. 2013; 5(5):511-522.
69. Gu JM, Robinson JR, Leung SH. Binding of acrylic polymers to mucin/epithelial surfaces: Structure-property relationships. Crit Rev Ther Drug Carr Syst. 1988; 5:21-67.
70. Jacob S, Nair AB, Boddu SHS, Gorain B, Sreeharsha N, Shah J. An updated overview of the emerging role of patch and film-based buccal delivery systems. Pharmaceutics. 2021; 13(8):1206.
71. Tzanova MM, Hagesaether E, Tho I. Solid lipid nanoparticle-loaded mucoadhesive buccal films - Critical quality attributes and *in vitro* safety & efficacy. Int J Pharm. 2021; 592:120100.
72. Hazzah HA, Farid RM, Nasra MM, El-Massik MA, Abdallah OY. Lyophilized sponges loaded with curcumin solid lipid nanoparticles for buccal delivery: Development and characterization. Int J Pharm. 2015; 492(1-2):248-257.
73. Hazzah HA, Farid RM, Nasra MMA, Hazzah WA, El-Massik MA, Abdallah OY. Gelucire-based nanoparticles for curcumin targeting to oral mucosa: Preparation, characterization, and antimicrobial activity assessment. J Pharm Sci. 2015; 104(11):3913-3924.
74. Hazzah HA, Farid RM, Nasra MM, Zakaria M, Gawish Y, El-Massik MA, *et al*. A new approach for treatment of precancerous lesions with curcumin solid-lipid nanoparticle-loaded gels: *In vitro* and clinical evaluation. Drug Deliv. 2016; 23(4):1409-1419.
75. Nidhi M, Patro MN, Kusumvalli S, Kusumdevi V. Development of transmucosal patch loaded with anesthetic and analgesic for dental procedures and *in vivo* evaluation. Int J Nanomedicine. 2016; 11:2901-2920.
76. Karavana SY, Gökçe EH, Rençber S, Özbal S, Pekçetin C, Güneri P, *et al*. A new approach to the treatment of recurrent aphthous stomatitis with bioadhesive gels containing cyclosporine A solid lipid nanoparticles: *In vivo*/*in vitro* examinations. Int J Nanomedicine. 2012; 7:5693-5704.
77. Jones E, Ojewole E, Kalhapure R, Govender T. *In vitro* comparative evaluation of monolayered multipolymeric films embedded with didanosine-loaded solid lipid nanoparticles: A potential buccal drug delivery system for ARV therapy. Drug Dev Ind Pharm. 2014; 40(5):669-679.
78. Kraisit P, Yonemochi E, Furuishi T, Mahadlek J, Limmatvapirat S. Chitosan film containing antifungal agent-loaded SLNs for the treatment of candidiasis using a Box-Behnken design. Carbohydr Polym. 2022; 283:119178.
79. Holpuch AS, Hummel GJ, Tong M, Seghi GA, Pei P, Ma P, *et al*. Nanoparticles for local drug delivery to the oral mucosa: Proof of principle studies. Pharm Res. 2010; 27:1224-1236.
80. Zewail MB, Asaad GF, Swellam SM, Abd-Allah SM, Hosny SK, Sallah SK, *et al*. Design, characterization and *in vivo* performance of solid lipid nanoparticles (SLNs)-loaded mucoadhesive buccal tablets for efficient delivery of lornoxicam in experimental inflammation. Int J Pharm. 2022; 624:122006.
81. Ho HN, Le HH, Le TG, Duong THA, Ngo VQT, Dang CT, *et al*. Formulation and characterization of hydroxyethyl cellulose-based gel containing metronidazole-loaded solid lipid nanoparticles for buccal mucosal drug delivery. Int J Biol Macromol. 2022; 194:1010-1018.
82. Hosny KM, Naveen NR, Kurakula M, Sindi AM, Sabei FY, Fatease AA, *et al*. Design and development of neomycin sulfate gel loaded with solid lipid nanoparticles for buccal mucosal wound healing. Gels. 2022; 8:385.
83. Ding Y, Nielsen KA, Nielsen BP, Bøje NW, Müller RH, Pyo SM. Lipid-drug-conjugate (LDC) solid lipid nanoparticles (SLN) for the delivery of nicotine to the oral cavity - Optimization of nicotine loading efficiency. Eur J Pharm Biopharm. 2018; 128:10-17.
84. Severino P, Silveira EF, Vazzana M, Chaud MV, Santana MH, Souto EB. Validation of an UV spectrophotometric assay for the quantification of polymyxin B in solid lipid nanoparticles. Pharmazie. 2015; 70(11):693-697.
85. Murgia D, Angellotti G, D'Agostino F, De Caro V. Bioadhesive matrix tablets loaded with lipophilic nanoparticles as vehicles for drugs for periodontitis treatment: Development and characterization. Polymers. 2019; 11(11):1801.
86. Murgia D, Angellotti G, Conigliaro A, Carfi Pavia F, D'Agostino F, Contardi M, *et al*. Development of a multifunctional bioerodible nanocomposite containing metronidazole and curcumin to apply on L-PRF clot to promote tissue regeneration in dentistry. Biomedicines. 2020; 8(10):425.
87. Tetyczka C, Griesbacher M, Absenger-Novak M, Fröhlich E, Roblegg E. Development of nanostructured lipid carriers for intraoral delivery of Domperidone. Int J Pharm. 2017; 526(1-2):188-198.
88. Elkomy MH, Elmowafy M, Shalaby K, Azmy AF, Ahmad N, Zafar A, *et al*. Development and machine-learning optimization of mucoadhesive nanostructured lipid carriers loaded with fluconazole for treatment of oral candidiazis. Drug Dev Ind Pharm. 2021; 47(2):246-258.
89. Basahih TS, Alamoudi AA, El-Say KM, Alhakamy NA, Ahmed OAA. Improved transmucosal delivery of glimepiride via unidirectional release buccal film loaded with vitamin E TPGS-based nanocarrier. Dose Response. 2020; 18(3):1559325820945164.
90. Marques AC, Rocha AI, Leal P, Estanqueiro M, Lobo JMS. Development and characterization of mucoadhesive buccal gels containing lipid nanoparticles of ibuprofen. Int J Pharm. 2017; 533(2):455-462.
91. Ribeiro LNM, Franz-Montan M, Breitkreitz MC, Rodrigues da Silva GH, de Castro SR, Guilherme VA, *et al*. Nanohybrid hydrogels designed for transbuccal anesthesia. Int J Nanomedicine. 2018; 13:6453-6463.
92. Ribeiro LNM, Franz-Montan M, Alcântara ACS,

Breitkreitz MC, Castro SR, Guilherme VA, *et al*. Hybrid nanofilms as topical anesthetics for pain-free procedures in dentistry. Sci Rep. 2020; 10(1):11341.
93. Mendes AI, Silva AC, Catita JAM, Cerqueira F, Gabriel C, Lopes CM. Miconazole-loaded nanostructured lipid carriers (NLC) for local delivery to the oral mucosa: Improving antifungal activity. Colloids Surf B Biointerfaces. 2013; 111:755-763.
94. Hosny KM, Sindi AM, Ali S, Alharbi WS, Hajjaj MS, Bukhary HA, *et al*. Development, optimization, and evaluation of a nanostructured lipid carrier of sesame oil loaded with miconazole for the treatment of oral candidiasis. Drug Deliv. 2022; 29(1):254-262.
95. Rincón M, Espinoza LC, Silva-Abreu M, Sosa L, Pesantez-Narvaez J, Abrego G, *et al*. Quality by design of pranoprofen loaded nanostructured lipid carriers and their ex vivo evaluation in different mucosae and ocular tissues. Pharmaceuticals. 2022; 15(10):1185.
96. Kraisit P, Sarisuta N. Development of triamcinolone acetonide-loaded nanostructured lipid carriers (NLCs) for buccal drug delivery using the Box-Behnken design. Molecules. 2018; 23(4):982.
97. Ghasemiyeh P, Mohammadi-Samani S. Hydrogels as drug delivery systems; pros and cons. Trends Pharm Sci. 2019; 5(1):7-24.
98. Montenegro-Nicolini M, Morales JO. Overview and future potential of buccal mucoadhesive films as drug delivery systems for biologics. AAPS PharmSciTech. 2017; 18:3-14.
99. Rathbone MJ, Drummond BK, Tucker IG. The oral cavity as a site for systemic drug delivery. Adv Drug Deliv Rev. 1994; 13(1-2):1-22.
100. Satheesh Madhav NV, Semwal R, Kumar Semwal D, Semwal RB. Recent trends in oral transmucosal drug delivery systems: An emphasis on the soft palatal route. Expert Opin Drug Deliv. 2012; 9(6):629-647.
101. El-Nahas AE, Allam AN, El-Kamel AH. Mucoadhesive buccal tablets containing silymarin Eudragit-loaded nanoparticles: Formulation, characterisation and ex vivo permeation. J Microencapsul. 2017; 34(5):463-474.
102. Freitas C, Müller RH. Spray drying of solid lipid nanoparticles (SLN^{TM}). Eur J Pharm Biopharm. 1998; 46(2):145-151.
103. Pinto JF, Müller RH. Pellets as carriers of solid lipid nanoparticles (SLN) for oral administration of drugs. Pharmazie. 1999; 54:506-509.
104. Magalhães AP, Toma HK, do Carmo FA, Mansur CR. Development of purified cashew gum mucoadhesive buccal tablets containing nystatin for treatment of oral candidiasis. Drug Dev Ind Pharm. 2021; 47(5):825-837.
105. Woolfson AD, Umrethia ML, Kett VL, Malcolm RK. Freeze-dried, mucoadhesive system for vaginal delivery of the HIV microbicide, dapivirine: Optimisation by an artificial neural network. Int J Pharm. 2010; 388(1-2):136-143.