REVIEW ARTICLE

Improvements in Transdermal and Mucosal Medication Methods of Administration using Nanoparticulates

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Abstract

Regarding both regional as well as widespread drug delivery, the mucosal and buccal modes of consumption offer a number of benefits. In particular, when a rapid beginning of action must be achieved, they have proven to be an effective rival to the conventional oral approach. Drugs can be easily abused by veins that drain to the elevated and immediately assimilated into circulation throughout the body. In light of this, they are helpful for medicines with high clearance through the liver or digestion in the alimentary canal, as well as for people who have trouble gulping it down. The usual formulation of medications for use with the sublingual and buccal routes is a solid medication. Dosage forms are made of liquid (such as sprays), and dosage forms in a variety of sizes of tablets, wafers, films, patches dose forms that are partially solid (such as gels and drops), and tablets. Standard dosage types include. The biological factors are frequently impacted, which can decrease the formulation's proximity to the skin. A mucosa could cause unpredictably high medication retention. Numerous things have happened for composition improvements to increase the utilization and retention of medicines in the buccal area and the sublingual area. The physiologic components that will be covered in this primer the development of nanoparticulate delivery systems for drugs, and how it affects buccal and sublingual administration of drugs ways to administering sublingually and buccally therapeutic advancement pathways with compositions that have passed testing for clinical approval will also be covered.

Key words: Buccal, creation, delivery of medication, mucosal, nanoparticles, physiological variables, sublingual

INTRODUCTION

Medications are typically injected into the mouth with the aim of treating local diseases (such as allergies and lesions) or helping the body absorb them. Particularly vascularized and advantageous for systemic medication administration are the sublingual and buccal epithelial areas. Sublingual medication beneath the tongue for governance, and behind the gums for buccal administration. A substance beneath the surface of the cheek and gums. The buccal and sublingual pathways are viewed to be exciting substitutes for the conventional oral medication release method. A schematic illustration of the lateral and sublingual areas of the mouth cavity is shown in Figure 1. The pH of the cavity in the mouth ranges from 6.2 to 7.4, and there is little enzyme production. The buccal and sublingual surfaces make up the majority of the oral mucosa's area of coverage, which ranges from 100 to 200 cm^2. Which, according to,[12] have approximate areas of 2.9 cm^2 and 4.2 cm^2, accordingly. Non-keratinized skin lines these areas of the mouth cavity in the sublingual area, divided squamous epithelium with a thickness of 8–12 cells and 100–200 m, The buccal region is 500–800 m and 40–50 cells thick.[12]

A mucus coating with a median thickness varying from 70 to 100 m is produced by salivary ingredient adhesion to the buccal and sublingual tissues.[36] The propria, lamina, and

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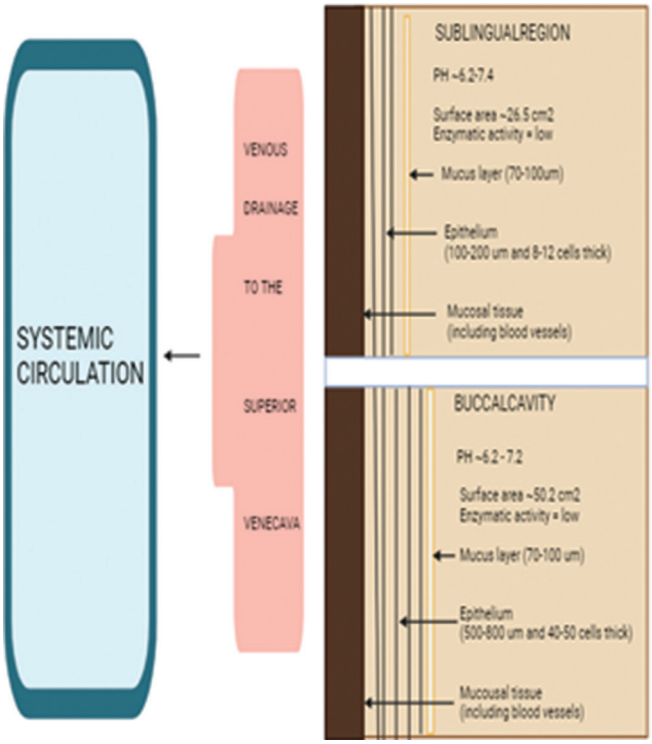

Figure 1: Sublingual and buccal portions of the mouth cavity are shown in a simplified diagram

submucosa, which are made of elastic tissue and have an arrangement of veins, lymphatic vessels, and soft muscle fibers, are located beneath the skin's epithelium.[8] Through veins that lead to the top of the vena cava, medications can be swiftly and effectively incorporated into the circulation throughout the body.[21] Sublingual and buccal drug administration has seen a lot of improvements in drug composition.[26] The improvements in nanoparticulate drug delivery techniques for sublingual and swallowing will be the main topics of this review, which will also cover biological variables that affect buccal and sublingual drug delivery.[37]

THE BENEFITS AND DRAWBACKS OF THE SUBLINGUAL AND BUCCAL ROUTES FOR DRUG DELIVERY

For persistent medication delivery, the sublingual and buccal modes of dispensing have an assortment of benefits.[15,36] In most cases, they result in a faster start of effect than medicine formulas taken orally. Because of the brittle epithelium, the absorption of drugs occurs through the sublingual mucosa more quickly than the buccal mucosa. Despite rapidly entering the bloodstream, the drug's arterial reception also avoids the liver's first-pass process of metabolism and enters the circulation throughout the body directly. Because of this, this method is especially beneficial for exceptionally soluble medications that have an elevated probability of elimination from the liver or digestive tract degradation. Reduced mucin and fewer enzymes, such as amylase, a salivary enzyme, also exist in the inflexible saliva in the buccal and sublingual areas. In addition, because the pH in the salivary glands is more balanced than in various parts of the stomach and intestines, drugs might remain more stable there. Patients are able to administer medications with ease, and on the majority of occasions, merely by swallowing or throwing up the pill, for instance, the impact of the drug may be quickly neutralized. It could be helpful for those who have difficulty swallowing. Patients may experience discomfort while using the sublingual and buccal techniques since they must follow specific legal measures to maintain the medicines in the sublingual or buccal area for successful assimilation instead of swallowing. Not every medicine can be delivered in this method, and usually, only small quantities can. Particular medications may also taste bad, bitter, or aggravate the oral mucosa, that can cause either deliberate or unintentional vomiting. Despite the low hazards, there is still a chance of inadvertent medication demand. Patients are warned to be standing while taking the medicine as an outcome. Sublingual or buccal medication should not be administered to a patient who is groggy or stubborn because these symptoms have the same underlying causes.[15,36]

HYPOTHERAPEUTIC FACTORS IMPACTING SUBLINGUAL AND BUCCAL DRUG DELIVERY

Numerous biological variables should be taken into account while designing and developing medication formulations for sublingual or buccal drug delivery. The accessibility, equilibrium, effectiveness, and reliability of medicine may be impacted by the aforementioned variables.

Dwelling duration of the formulation

How long a medicine stays in the sublingual and buccal areas affects absorption significantly. According to the patient and the formulation, this can change significantly. Typically, medications for buccal and sublingual administration come in the shape of pills, films, wafers, or sprays. When it comes to a requirement for breakdown and deconstruction before drug absorption, the formulations vary. Furthermore, patients must wait until the drug has been assimilated before eating, drinking, chewing, or swallowing. The medication's potency will be reduced if it is swallowed. Particularly gets difficult for youngsters.[1,15]

Drug intake

The drug must possess an appropriate mixture of hydrophilic and lipophilic characteristics for absorption to be prosperous.[1,15] To be capable of traversing the epidermal barrier in these areas – which is typically accomplished by apathetic diffusion – the medicine must be accessible in

aquatic buccal secretions and also have a substantial lipid permeability. The low to intermediate molecular weight medications are also better suited to this pathway.

In addition, if there are open wounds or inflammatory lesions on the tissues of the mouth or gums, this can impair how well a medicine is absorbed. It is best to refrain from using this or employ it sparingly as it may result in heightened or inconsistent drug absorption. Contrarily, smoke can reduce the effectiveness of medicines through the sublingual or buccal routes due to vascular vasoconstriction [Table 1].[15]

Salivary PH

Salivary pH level may have an effect on how well drugs are absorbed by altering the state of ionization of medicines. Drug compounds quietly soak into tissues primarily through paracellular or transcellular transport, depending on its chemical and biological features. The transcellular dissemination mechanism, which occurs most often, has a strong correlation with the drug's capacity to disintegrate in lipids. Penetration is promoted whenever the medication component is in its non-ionized form since it is considerably more lipophilic compared to its ionized form.[15] Salivary has a relatively neutral pH, that makes it perfect for sublingual and buccal delivery and prefers drugs with an increased pKa factor.

The paracellular pathway is favorable to substances that are more permeable or cationic. It is important to recognize that certain environmental (such as food and drink) or human variables (such as oral sickness, which can affect the sublingual and buccal absorption of drugs) may suddenly alter the pH of saliva.

Saliva flow

Saliva circulation can alter how quickly the mixture and medication disintegrate, therefore they have an impact on the buccal and sublingual delivery of drugs. In particular, a parched mouth may negatively impact the way a medication is consumed.

On the reverse side, excessive salivation could hinder the drug from being taken in and instead cause it to be swallowed. Salivary flow can be impacted by a number of factors, including age, medications (such as anticholinergics), and health issues (such as Sjögren's syndrome, cheilosis, glossodynia, a lack of water difficulty swallowing, and problems with mastication).[14,38]

APPROACHES FOR DELIVERING NANOPARTICULATE DRUGS

In the past, it has been demonstrated that nanoparticulate systems can enhance the formation, utilization, and absorption of medications over a number of physiological barriers, such as the digestive system[19] and skin.[20] Hence, research into nanoparticles for buccal and sublingual medication administration was unavoidable. By packing the medicinal product or ingredient of interest into nanoparticles before dispersing them in a solution base,[17] nanoparticulate dosages are distinct from traditional forms of administration.[1] For sublingual and buccal delivery of medicines, they are integrated into a variety of dosage forms, such as gels, sprays, tablets, films, and patches.[6,16]

Table 1: Commercialized and being tested in clinical studies are sublingual and buccal versions

Drugs	Dosage forms	Indications	Status
Lorazepam	Tablet	Sedation	Marketed (Ativan)
Zolpidem	Tablet	Insomnia	Marketed (Edluar)
Melatonin	Tablet	Insomnia	Marketed (Melatonin Sublingual)
Allergen extract	Tablet	Allergic rhinitis	Marketed (Grastek, Oralair, Odactra, Ragwitek)
Polyvalent mechanical bacterial lysate (biological)	Tablet	Chronic obstructive pulmonary disease	Marketed (Ismigen)
Buprenorphine	Tablet, film	PAIN	Marketed (Temgesic, Belbuca)
Vitamin B12 tablet, spray, oral liquid vitamin deficiency (Sublingual Vitamin B12)	Tablet, spray, oral liquid	Vitamin deficiency	Sublingual Vitamin B12)
Tizanidine	Powder	Muscle spasticity	Phase I/II completed
Triamcinolone	Paste	Oral ulceration	Marketed (Kenalog in Orabase)
Influenza vaccine	Oral liquid	Healthy	Phase I completed
Naloxone	Oral liquid	Chronic pruritus	Phase I/II completed
Polyoxidonium	Spray	Acute respiratory infection	Phase III
Flumazenil	Spray	Healthy	Phase I/II completed
Apomorphine	Film	Parkinson's disease	Phase II/III

These nanoparticulate products have been experimentally demonstrated to:

1. Increase drug accessibility among the epithelium
2. Alter the rate at which drugs are released (e.g., controlled release or endured release)
3. Transmit solubilization (i.e., deliver molecules whose physical and chemical characteristics severely restrict their aqueous solubility)
4. Preserve substances which vulnerable to deterioration (e.g., peptides).

These elements work to increase the medications' sublingual or buccal bioavailability for later gastrointestinal absorption.[18]

To be effective for sublingual or buccal delivery of drugs, nanoparticulate compositions have to take into consideration two essential factors. Take into account the chemical and physical elements of the nanomaterials oneself, including dimensions, control, structure, and external properties, to determine the point of contact that will work optimally alongside the sublingual or buccal mucosa. The most common kinds of nanoparticulate systems being studied for buccal and sublingual medicine delivery are those that utilize lipid and polymeric components. By changing the composition and structure of micron-sized particles a number of different properties can be given, including mucoadhesion, bioadhesion, mucus-penetration, regulated dispersion, and the tendency to distort. In one instance, it has been discovered that encapsulating nanoparticles with polymeric polyethylene glycol improves the way they travel through lymphatic routes and their ability to enter vessels that carry lymph.

The majority of research studies in this field utilized nanoparticles with an ideal size ranging from 100 and 300 nm for sublingual or buccal delivery.[10] The proper interaction with the buccal or sublingual mucosa has only been thoroughly examined in an extremely limited amount of trials. The ability of neutral polyethylene nanoparticles (25, 50, and 200 nm) dispersed in a water-based base to pass through into the mucosal tissue unaltered was, for instance, shown through studies conducted *in vivo* employing porcine buccal mucosa. The 200 nm-sized nanoparticles were capable of breaking down more quickly and into more deeply embedded areas of the mucosa. The tiny nanoparticles were thought to be easily caught and stabilized in the mucus matrix. This is further reinforced by research, which demonstrated that unaltered healthy human oral mucous membranes taken from patients undergoing surgery could be penetrated by 200-nm nanoparticles (FluoSpheres® polyethylene nanoparticles) through the layer of epithelium and basement layer into the connective tissue that lies beneath.[11] It must be highlighted both of the experiments utilized polypropylene nanoparticles, which cannot be digested and can disrupt cell metabolic processes. To assess the impact of more therapeutically applicable nanoparticulate components over a variety of size ranges. It could be beneficial to conduct additional studies on mucosal porosity and absorption of drugs for oral and sublingual delivery of drugs. Concerning how the charged surface affects how nanoparticles engage with the oral mucosa, there are contradicting findings. The ability of 20 nm anionic (negatively charged) and 200 nm cationic (positively charged) nanoparticles to penetrate the mucus membrane of swine buccal mucosa was demonstrated.[30] Relative to the 20 nm anionic nanoparticles, which stayed in the highest 1/3 of the epithelium, the cationic nanoparticles (200 nm) penetrated the buccal mucosal tissue further.[5] According to the findings, 200 nm anionic nanoparticles created aggregates amid the mucus and were unlikely to pass through the epithelium.[9] Noted identical variations in the mucosa's connection to nanoparticles of opposing charges.

Nevertheless, according to certain research[10,13] cationic nanoparticles bind to mucus more extensively and possess lesser mucosal transparency than anionic nanoparticles.[41] Work in the tissues of the lower intestinal tract has shown that cationic nanoparticles and antagonistic mucins may collaborate electrostatically to prevent the passage of the nanoparticles across the mucus layer.[20] The chemical reaction of the nanoparticles with the composition of the substrate is a second crucial aspect that needs to be taken into account for successful sublingual or buccal medication delivery. When integrated into the pharmacological foundation, the nanoparticles should be resilient, notably throughout manufacture and transportation. To maximize medication porosity and absorption into the body, the product's base should also lengthen the duration the preparation spends in the sublingual or buccal area.[20] Regarding the factual interface of the formulations including nanoparticles with the mucosal tissue, there are conflicting data.[16,17] Most investigations have shown prolonged drug dispersion from the recommended dosage form's contained nanoparticles, after which the medication diffuses into the formulation base and gets utilized by the adherent mucosa.[25,27] This involves gels that have nanoparticles in them.[1] Sprays, tablets, films, and patches.[6]

Just a tiny amount of study has been done to confirm the ingestion of uninjured nanomaterials by mucosa and the ejection of nanomaterials from the formulation base for drug administration. As an example, researchers have developed technologically whirled nanofiber-based mucus adhesive films that have three distinct layers: An adhesive-based film layer, an insulation bolstering layer along with, and a layer that serves as reservoirs for micron-sized particles that are quickly preserved to the nanofibers' exterior layers or deposited in their interior minuscule areas.[25] The results of the *in vivo* and *ex vivo* tests performed on pork revealed that the nanofibrous mucous binding films were having the ability to maintain a prolonged variability in the proportion of the nanoparticles at the depth of the mucous membrane and ensure unidirectional dispersion throughout the cavity's contents.

The mucosa and nearby lymphatic vessels were penetrated by entire nanoparticles in biopsy specimens taken 2 h post-*in vivo* delivery.[18]

It is yet unclear whether nanomaterials used for sublingual or buccal administration of drugs behave differently when provided in an aqueous base (such as water or a neutralized solution) or when incorporated into a compound's base (such as films, gels, or tablets).[1] If nanomaterials are employed as a scaffolding to increase stability and regulate the rate of drug release from inside the formulation base or after mucosal penetration as pristine particulates, greater study is required to identify which is most advantageous.[22] While the second approach would focus more emphasis on physical attributes, the preceding technique might put more emphasis on the persistence of the formulation base on the mucosa and the stability of the nanoparticles in the formulation base for releasing the drug.[23] There are very few *in vivo* research readily accessible, and the majority of investigations have been solely performed *in vitro* and/or *ex vivo* models. Given that, as was already said, there are a lot of physiological parameters that have an impact on medication absorption, in *in vivo* investigations offer more information about the formulation's efficacy in real-world settings. The sublingual and buccal mucosa of various creatures varies significantly anatomically as well. Although rodents with hydrated mucosa are more frequently utilized in *in vivo* research than swine mucosa, which is the mucosa that is most analogous to human mucosa.[22,39] When assessing the outcomes, it is important to keep in mind that keratin formation of the mucosa creates another obstacle to the absorption of medications and nanoparticles. The application of nanoparticulate drug delivery techniques for sublingual and buccal administration is supported by scientific evidence to date, but more thorough biochemical and translational investigations are needed to assure consistency of safety and effectiveness outcomes.[40]

APPROVED FOR USE IN CLINICAL TRIALS AND SUBLINGUAL AND BUCCAL FORMULAS

There are several sublingual and buccal preparations available, and further ones are being developed clinically. Exemplary examples of authorized or undergoing research studies for sublingual and buccal formulations are shown in Table 1. Sedation, sleeplessness, cardiac arrest, agony, and quitting smoking are some of the many possibilities for those who were recently given the go-ahead for clinical application.[29] These reasons also profit from the speedier initial action. It is possible to employ medications with limited efficacy and for prolonged use since the medicines' clinical indices and regimens differ. In addition, biological materials have entered the sector in the form of extracts of allergens and polyvalent biomechanical microbial lysate, which are used to treat rhinitis caused by allergies and persistent obstructive pulmonary disease (COPD), accordingly used, and is typically included. Drugs are typically included in traditional dosage forms that consist of tablets, wafers, lozenges, films, sprays, and oral liquid drops as well as semi-solid dosage forms such as gels and paste in sublingual and buccal formulations that are authorized for use in clinical trials.[1] To facilitate quick absorption of medicines through the mucosa without the use of fluid, solid dosage forms are frequently created to crumble or break down quickly with a tiny amount of saliva.[2,3] The drug is either disintegrating (referred to as a solution) or distributed (referred to as a suspension) in a carrier in liquid dosage forms intended for sublingual and buccal usage. Following this, it is given as oral liquid drops or sprays, with the latter frequently having a calibrated device to regulate the dose of the medication dispensed.

In a significant number of research trial formulations [Table 1], commonly used sublingual and buccal dosage forms – particularly tablets, films, and oral liquids – incorporate already-approved medications or newly developed chemicals. It needs to be mentioned that medications assessed during the preliminary stages of research in clinical trials are frequently given as an oral powder or liquid. In contrast to oral liquids, which are created by distributing powder into a liquid basis or by employing the medication's injectable compositions, powders are normally created by cracking open therapeutically accessible capsules or smashing tablets. As opposed to analyzing the effectiveness of innovative formulations, the main objective of this research is on measuring the pharmacokinetics and efficiency of the drug after sublingual or buccal delivery. Only a few novel forms of administration for buccal and sublingual delivery of drugs have advanced to the point of clinical development.

The main tactics comprised adding mucous adhesive or permeation-enhancing components to traditional dose formulations. Biological processes (such as saliva and swallowing) frequently have an impact on traditional dose forms, which might diminish the formulation's interaction with the mucosa and result in unexpected medication assimilation. In addition, there may be less medication penetration in the sublingual and buccal epithelium due to its multilayer density and stacked structure.[46] It has been demonstrated that using these techniques will increase the porosity and/or mucosal persistence of traditional dose forms. For instance, it has been demonstrated that permeation-enhancing substances (such as surfactants, bile salts, fatty acids, cyclodextrins, and chelators) increase mucosal susceptibility and absorption of various compounds.[33]

The thermodynamic action of medications is increased through

1. Altering the viscosity of mucus
2. Enhancing the flexibility of the bilayer of lipids membrane
3. Affecting the elements at narrow junctions

4. Suppressing mucosal proteins and
5. Impacting on the elements at close junctions.[34]

In addition, it has been shown that including mucous adhesive ingredients improves formulation persistence with the sublingual or buccal mucosa.[35]

Solid and semi-solid dosage forms have generally been the focus of this work. These solutions frequently use mucous adhesive polymers, such as those derived from organic compounds such as chitosan, hyaluronic acid, agarose, and different gums, as well as artificial polymers such as cellulose derivatives and poly(acrylic acids)-based polymers.[7,28] To enable the bidirectional distribution of drugs, an impenetrable covering coating may be added to solid dosage forms (such as films, patches, and tablets).[45] It is anticipated that after thorough preclinical analysis and effectiveness, further novel dosage formulations could ultimately participate in clinical studies. This comprises compositions with nanoparticulates, particularly for the systemic delivery of medications.[33,38]

The only nanoparticulate preparation that has been tested in clinical research for buccal and sublingual administration of medications is the ropivacaine liposomal gel. In the initial phase of clinical research, it has been assessed for topical anesthesia and local medication administration. In addition, to speed up or regulate the dissipation of biological ingredients over an extended amount of time, slow-disintegrating and non-disintegrating dosages, notably for mucosal drug administration, have undergone extensive examination in the scientific community.[31] For instance, laminated coatings have been produced for the controlled administration of drugs, and they have a tendency to stay intact in their original state and emit medicine throughout a certain time.[42] It must be stated that compositions that come into touch with the mouth mucosa for an extended period may irritate and/or pain to the individual taking them, particularly if they are taken along with a meal or a beverage.[24] In addition, there is a chance that the dosage form will separate from the mucosa and be ingested, which might result in adhesion to additional digestive tract regions (such as the esophageal).[24] The viability of these dose formulations in clinical settings will be decided by the findings of the clinical investigations.[32]

CONCLUSION

For widespread drug distribution, the sublingual and buccal modes of consumption have many benefits. They have proven to be a successful substitute for the conventional oral route, particularly when a rapid beginning of the process is essential.[43] They are also helpful for people who struggle to swallow and for medications that are highly cleared by the liver or degraded in the digestive tract.[40] Few notable advancements in medication formulation have made it to the therapeutic stage, despite substantial improvements in persistence and bioavailability in the buccal and sublingual areas having been described in research. Every novel drug composition must clearly outperform presently accessible forms of administration in terms of effectiveness and/or risk in order for clinical application to be validated.[19,20]

According to the applicable laws and regulations, thorough assessments of the compositions' pharmacokinetics, equilibrium, efficiency, and risk are also necessary in suitable model organisms and clinical investigations.[44] Additional study is required to determine the principle of action and security of various transporters after mucosal contact and/or absorption for revolutionary technologies such as nanotechnology.[4] Independent of a drug's effectiveness in therapy, the intricate nature of its composition is another important aspect that may operate as a roadblock to its clinical implementation. To enable effective and repeatable massive amounts of production, formulation development must be simplified. The lack of uniform testing processes may also make it difficult to accurately evaluate the efficacy of greater complexity or novel products for regulated criteria.

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