



INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES

Intra oral sprays -An overview

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Abstract

Over the last three decades, intraoral dosage forms have been evolving as an acceptable and in some cases as the preferred, alternative to conventional tablets and capsules. Among them, Oral sprays are the fastest, most effective and comfortable way to take medicines, nutrients, minerals and vitamins. They have been acquiring important position in the market by overcoming previously encountered administration problems and contributing to extension of patent life. Oral sprays have the unique property of rapidly releasing the drug in the oral cavity, thus obviating the requirement of water during administration. Therefore, these dosage forms have lured the market for a certain section of the patient population which includes dysphagic, bed ridden, and psychic, geriatric patients. This article focuses on the transmucosal view, spray formulation aspects, advances made so far in the field oral sprays and patented technologies.

Key-Words: Intra oral dosage form, Oral sprays, quick release.

Introduction

For years, millions of us have taken pills to supplement our nutritional needs, to cure a headache, flu or the emergency attacks. We have created a ritual of gulping them down with a glass of water that leaves a chalky taste in our mouths, or even having them get caught in our throat. No matter the size or shape, whether gel caps or coated tablets, it's not an easy task. Difficulty in swallowing conventional tablets and capsules is common among all age groups, especially in elderly and dysphagic, heart, insomnia and diabetic patients.¹ One study showed that 26% out of 1576 patients experienced difficulty in swallowing tablets due to their large size, followed by their surface, shape and taste.² Elderly patients may find the administration of the conventional oral dosage forms difficult as they regularly require medicines to maintain a healthy life.^{3,4} Children may also have difficulty in ingesting because of their underdeveloped muscular and nervous systems.⁵

The problem of swallowing tablets is also evident in travelling patients who may not have ready access to water.⁶ Many people do not take medicines simply because they cannot or do not like to swallow pills. That loss could have a negative effect on one's health.

The oral cavity (OC) and its highly permeable mucosal tissues have been taken advantage of for decades as a site of absorption for delivery of drugs to the systemic circulation (oral transmucosal delivery, OTD), and for local delivery to the subjacent tissues (oral mucosal delivery, OMD). Administration of an active agent in a dosage form intended to release the drug in the oral cavity is referred as an intraoral delivery system or intraoral dosage form (IOD).

The first evidence of drug absorption via the buccal mucosa was noted over 100 years ago.¹⁹ Subsequently, in 1879, sublingual administration of nitroglycerin was reported to successfully alleviate the symptoms of classic angina pectoris.²⁰ Since then, oral mucosal drug delivery has drawn more and more attention because of its potential advantages over other routes of delivery. The concept of an aerosol originated as early as 1790, when self-pressurized carbonated beverages were introduced in France.⁷ Oral sprays are the fastest, most effective and convenient way to get a daily dose of vitamins, minerals, and other nutritional supplements. The design of oral sprays came out with a purpose to improve patient's compliance. These dosage forms rapidly release the drug in intra oral cavity, thus obviating the need for water during administration, an attribute that makes them highly attractive for paediatric and geriatric patients who need frequent or immediate medical intervention. Aforementioned problems can be resolved by means of Oral sprays.

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Oral sprays are known by various names aerosol sprays, liquid pump sprays, or activated mists. The CDER Data Standards Manual defines the term Oral sprays "A unit actuation pump or aerosol spray in a gas or solvent carrier vehicle for rapid drug absorption by the buccal mucosa".⁸ Suitable drug candidates for such systems include neuroleptics, cardiovascular agents, antidiabetic, analgesics, antihistergics, and drugs for erectile dysfunction.⁵ Oral spray offers several advantages over other dosage forms like ODTs, effervescent tablets, dry syrups and chewing gums/tablets, which are commonly used to enhance patient's compliance. Administering effervescent tablets/granules and dry syrups involve unavoidable preparation that include the intake of water. Elderly patients cannot chew large pieces of tablets or gums and sometimes experience the bitter or unpleasant taste of the drug in the dosage forms if the taste masking coat ruptures during mastication. Oral spray releases medicament rapidly in the form of micro sized droplets in intra oral cavity to be absorbed by buccal mucosa, a direct and rapid dispersion of a solution of the active agent over as large a portion as possible of the oral mucosa, which absorbs the active agent. In this way, a large area would be reached, thereby accelerating absorption of the active agent. Since the release medicament is in small droplet form, water is not required during administration.⁹ Within the oral mucosal cavity, the delivery of drugs is classified into two categories: (i) local delivery and (ii) systemic delivery either via the buccal or sublingual mucosa. This review presents the physiological considerations of the oral cavity in light of systemic drug delivery and provides an insight into the advances in oral sprays.

The present article provides brief view of oral mucosa and Physiological barriers for oral transmucosal drug delivery. Formulation of oral aerosol products is discussed along with marketed preparations. Later in this section a summary of research and patented technologies are discussed.

Advantages of oral sprays extent this phenomenon affects the efficiency of oral transmucosal

1. The intraoral or sublingual spray method of delivery is also very helpful for individuals who have difficulty swallowing pills or capsules and, since a lower dosage is required, it is cost effective.
2. Potential faster absorption could translate into faster onset of action.
3. Patient's compliance for disabled bedridden patients and for travelling and busy people who do not have ready access to water.¹⁰

4. Ease of administration to patients who cannot swallow, such as the elderly, stroke.
5. Victims and bedridden patients; patients who should not swallow, such as renal failure patients; and who refuse to swallow, such as pediatrics, geriatric and
6. psychiatric patients.^{11, 12}
7. Pre gastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.¹³
8. New business opportunities: product differentiation, line extension and life-cycle management, exclusivity of product promotion and patent-life extension.^{12, 14}
9. Sprays do not contain fillers or binders, contrary to the make-up of pills, providing exclusion of additional excipients.

Overview of the oral mucosa

The oral cavity comprises the lips, cheek, tongue, hard palate, soft palate and floor of the mouth (Fig. 1). The lining of the oral cavity is referred to as the oral mucosa, and includes the buccal, sublingual, gingival, palatal and labial mucosa. The buccal, sublingual and the mucosal tissues at the ventral surface of the tongue account for about 60% of the oral mucosal surface area. The top quarter to one-third of the oral mucosa is made up of closely compacted epithelial cells (Fig. 2). The primary function of the oral epithelium is to protect the underlying tissue against potential harmful agents in the oral environment and from fluid loss. Beneath the epithelium is the basement membrane, lamina propria and submucosa. The oral mucosa also contains many sensory receptors including the taste receptors of the tongue. Three types of oral mucosa can be found in the oral cavity; the lining mucosa is found in the outer oral vestibule (the buccal mucosa) and the sublingual region (floor of the mouth) (Fig. 1). The specialized mucosa is found on the dorsal surface of tongue, while the masticatory mucosa is found on the hard palate (the upper surface of the mouth) and the gingiva (gums). The lining mucosa comprises approximately 60%, the masticatory mucosa approximately 25%, and the specialized mucosa approximately 15% of the total surface area of the oral mucosal lining in an adult human. The masticatory mucosa is located in the regions particularly susceptible to the stress and strains resulting from masticatory activity. The superficial cells of the masticatory mucosa are keratinized, and a thick lamina propria tightly binds the mucosa to the underlying periosteum. Lining mucosa on the other hand is not nearly as subject to masticatory loads and

consequently, has a non-keratinized epithelium, which sits on a thin and elastic lamina propria and a submucosa. The mucosa of the dorsum of the tongue is a specialized gustatory mucosa, which has well papillated surfaces; which are both keratinized and some non-keratinized.

Physiological barriers for oral transmucosal drug delivery

The environment of the oral cavity presents some significant challenges for systemic drug delivery. The drug needs to be released from the formulation to the delivery site (e.g. buccal or sublingual area) and pass through the mucosal layers to enter the systemic circulation. Certain physiological aspects of the oral cavity play significant roles in this process, including pH, fluid volume, enzyme activity and the permeability of oral mucosa. The principle physiological environment of the oral cavity, in terms of pH, fluid volume and composition, is shaped by the secretion of saliva. Saliva is secreted by three major salivary glands (parotid, sub maxillary and sublingual) and minor salivary or buccal glands situated in or immediately below the mucosa. The parotid and sub maxillary glands produce watery secretion, whereas the sublingual glands produce mainly viscous saliva with limited enzymatic activity. The main functions of saliva are to lubricate the oral cavity, facilitate swallowing and to prevent demineralization of the teeth. It also allows carbohydrate digestion and regulates oral microbial flora by maintaining the oral pH and enzyme activity. The daily total salivary secretion volume is between 0.5 and 2.0 l. However, the volume of saliva constantly present in the mouth is around 1.1 ml, thus providing a relatively low fluid volume available for drug release from delivery systems compared to the GI tract. Compared to the GI fluid, saliva is relatively less viscous containing 1% organic and inorganic materials. In addition, saliva is a weak buffer with a pH around 5.5–7.0. Ultimately the pH and salivary compositions are dependent on the flow rate of saliva which in turn depends upon three factors: the time of day, the type of stimulus and the degree of stimulation. For example, at high flow rates, the sodium and bicarbonate concentrations increase leading to an increase in the pH. Saliva provides a water rich environment of the oral cavity which can be favorable for drug release from delivery systems especially those based on hydrophilic polymers. However, saliva flow decides the time span of the released drug at the delivery site. This flow can lead to premature swallowing of the drug before effective absorption occurs through the oral mucosa and is a well accepted concept known as “saliva wash out”.

However, there is little research on to what delivery from different drug delivery systems and thus further research needs to be conducted to better understand this effect. Drug permeability through the oral (e.g. buccal/sublingual) mucosa represents another major physiological barrier for oral transmucosal drug delivery. The oral mucosal thickness varies depending on the site as does the composition of the epithelium. The mucosa of areas subject to mechanical stress (the gingiva and hard palate) is keratinized similar to the epidermis. The mucosa of the soft palate, sublingual, and buccal regions, however, are not keratinized. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia do not contain acylceramides and only have small amounts of ceramides. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia. Within the oral mucosa, the main penetration barrier exists in the outermost quarter to one third of the epithelium. The relative impermeability of the oral mucosa is predominantly due to intercellular materials derived from the so-called membrane coating granules (MCGs). MCGs are spherical or oval organelles that are 100–300 nm in diameter and found in both keratinized and non-keratinized epithelia. They are found near the upper, distal, or superficial border of the cells, although a few occur near the opposite border. Several hypotheses have been suggested to describe the functions of MCGs, including membrane thickening, cell adhesion, and production of a cell surface coat, cell desquamation and as a permeability barrier. Hayward summarized that the MCGs discharge their contents into the intercellular space to ensure epithelial cohesion in the superficial layers, and this discharge forms a barrier to the permeability of various compounds. Cultured oral epithelium devoid of MCGs has been shown to be permeable to compounds that do not typically penetrate the oral epithelium. In addition, permeation studies conducted using tracers of different sizes have demonstrated that these tracer molecules did not penetrate any further than the top 1–3 cell layers. When the same tracer molecules were introduced sub-epithelial, they penetrated through the intercellular spaces. This limit of penetration coincides with the level where MCGs are observed. This same pattern is observed in both keratinized and non-keratinized epithelia, which indicates that MCGs play a more

significant role as a barrier to permeation compared to the keratinization of the epithelia. The cells of the oral epithelia are surrounded by an intercellular ground substance called mucus, the principle components of which are complexes made up of proteins and carbohydrates; its thickness ranges from 40 to 300 μm . In the oral mucosa, mucus is secreted by the major and minor salivary glands as part of saliva. Although most of the mucus is water ($\approx 95\text{--}99\%$ by weight) the key macromolecular components are a class of glycoprotein known as mucins (1–5%). Mucins are large molecules with molecular masses ranging from 0.5 to over 20 MDa and contain large amounts of carbohydrate. Mucins are made up of basic units ($\approx 400\text{--}500$ kDa) linked together into linear arrays. These big molecules are able to join together to form an extended three-dimensional network which acts as a lubricant allowing cells to move relative to one another, and may also contribute to cell–cell adhesion. At physiological pH, the mucus network carries a negative charge due to the sialic acid and sulfate residues and forms a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer. This gel layer is believed to play a role in mucoadhesion for drug delivery systems which work on the principle of adhesion to the mucosal membrane and thus extend the dosage form retention time at the delivery site. Another factor of the buccal epithelium that can affect the mucoadhesion of drug delivery systems is the turnover time. The turnover time for the buccal epithelium has been estimated to be 3–8 days compared to about 30 days for the skin.

Physiological opportunities for oral transmucosal drug delivery

Despite the challenges, the oral mucosa, due to its unique structural and physiological properties, offers several opportunities for systemic drug delivery. As the mucosa is highly vascularized any drug diffusing across the oral mucosa membranes has direct access to the systemic circulation via capillaries and venous drainage and will bypass hepatic metabolism. The rate of blood flow through the oral mucosa is substantial, and is generally not considered to be the rate limiting factor in the absorption of drugs by this route. For oral delivery through the GI tract, the drug undergoes a rather hostile environment before absorption. This includes a drastic change in GI pH (from pH 1–2 in the stomach to 7–7.4 in the distal intestine), unpredictable GI transit, the presence of numerous digestive enzymes and intestinal flora. In contrast to this harsh environment of the GI tract, the oral cavity offers relatively consistent and friendly physiological conditions for drug delivery which are maintained by

the continuous secretion of saliva. Compared to secretions of the GI tract, saliva is a relatively mobile fluid with less mucin, limited enzymatic activity and virtually no proteases. Enzyme degradation in the GI tract is a major concern for oral drug delivery. In comparison, the buccal and sublingual regions have less enzymes and lower enzyme activity, which is especially favorable to protein and peptide delivery. The enzymes that are present in buccal mucosa are believed to include aminopeptidases, carboxypeptidases, dehydrogenases and esterases. Aminopeptidases may represent a major metabolic barrier to the buccal delivery of peptide drugs. Proteolytic activity has been identified in buccal tissue homogenates from various species and a number of peptides have been shown to undergo degradation. The buccal and sublingual routes are the focus for drug delivery via the oral mucosa because of the higher overall permeability compared to the other mucosa of the mouth. The effective permeability coefficient values reported in the literature across the buccal mucosa for different molecules, range from a lower limit of 2.2×10^{-9} cm/s for dextran 4000 across rabbit buccal membrane to an upper limit of 1.5×10^{-5} cm/s for both benzylamine and amphetamine across rabbit and dog buccal mucosa, respectively. The oral mucosa is believed to be 4–4000 times more permeable than that of skin. Permeability of water through the buccal mucosa was approximately 10 times higher, whilst in floor of the mouth the permeability was approximately 20 times higher than skin. Drugs can be transported across epithelial membranes by passive diffusion, carrier-mediated active transport or other specialized mechanisms. Most studies of buccal absorption indicate that the predominant mechanism is passive diffusion across lipid membranes via either the paracellular or transcellular pathways, although these may actually be the same pathway. The hydrophilic nature of the paracellular spaces and cytoplasm provides a permeability barrier to lipophilic drugs but can be favorable for hydrophilic drugs. In contrast, the transcellular pathway involves drugs penetrating through one cell and the next until entering the systemic circulation. The lipophilic cell membrane offers a preferable route for lipophilic drugs compared to hydrophilic compounds. Drugs can transverse both pathways simultaneously although one route could be predominant depending on the physicochemical properties of the drug. Although passive diffusion is the predominant mechanism of absorption from the oral mucosa, specialized transport mechanisms have also been reported for a few drugs and nutrients. A study by Kurosaki and co-workers reported that the

rate of absorption of D-glucose from the dorsal and ventral surface of the tongue was significantly greater than that of L-glucose, which indicated the occurrence of some specialized transport mechanism. In addition, the existence of sodium-dependant D-glucose transport system was reported across stratified cell layer of human oral mucosal cells.²¹ The intra-oral method of absorption i.e. used in oral spray vitamins - has been shown to be up to 90% effective, whereas in (fig.3) The Physician's Desk Reference shows that vitamins and minerals in a pill form are only 10-20% absorbed by the body.³⁶

Factors Affecting Drug Absorption

Besides the biochemical characteristics of the buccal and sublingual membranes, which are responsible for the barrier function and permeability, various factors of the drug molecule influence the extent of permeation through the membranes. The lipid solubility, degree of ionization, pKa of the drug, pH of the drug solution, presence of saliva and the membrane characteristics, molecular weight and size of the drug, various physicochemical properties of the formulation, and the presence or absence of permeation enhancers, all affect the absorption and the permeation of drugs through the oral mucosa.

1. Degree of Ionization, pH, and Lipid Solubility

The permeability of unionizable compounds is a function of their lipid solubility, determined by their oil-water partition coefficients. The lipids present however contribute to this effect more in the keratinized epithelia (more total lipid content, nonpolar lipids, ceramides) than in the non keratinized epithelia where permeability seems to be related to the amount of glycosyl ceramides present. The absorption of drug through a membrane depends upon its lipophilicity, which in turn depends on its degree of ionization and partition coefficient. Generally small molecules that are predominantly lipophilic, with a log P of 1.6–3.3, are absorbed most rapidly; above 3.3, limited water solubility restricts their absorption. Most drugs delivered successfully via the buccal or sublingual route are therefore small and lipophilic (such as glyceryl trinitrate and nicotine), whereas large hydrophilic molecules are in general poorly absorbed.³⁰

The higher the unionized fraction of a drug, the greater is its lipid solubility. The degree of ionization in turn depends on the pH of the mucosal membrane and the pKa of the drug.²⁵ The pH of the mucosal surface may be different from that of buccal and sublingual surfaces throughout the length of the permeation pathway. Therefore, at neutral pH the preferred pathway was found to be transcellular, but at acidic pH, the ionized

species of the drug also contributed to the absorption across the membrane.

2. Molecular Size and Weight

The permeability of a molecule through the mucosa is also related to its molecular size and weight, especially for hydrophilic substances. Molecules that are smaller in size appear to traverse the mucosa rapidly. The smaller hydrophilic molecules are thought to pass through the membrane pores, and larger molecules pass extracellularly. Increases in molar volume to greater than 80 mL/mol produced a sharp decrease in permeability.^{26,27}

3. Permeability Coefficient

To compare the permeation of various drugs, a standard equation calculating the permeability coefficient can be used. One form of this equation is²⁸

$$P = \frac{\% \text{permeated} \times V_d}{A \times t \times 100}$$

where P is the permeability coefficient (cm=s), A is the surface area for permeation, V_d is the volume of donor compartment, and t is the time. This equation assumes that the concentration gradient of the drug passing through the membrane remains constant with time, as long as the percent of drug absorbed is small.

The primary challenges for these routes of delivery are:

1. The varying structure of the mucosal membrane in different parts of the oral cavity and the reduced permeation due to the barrier presented by the mucosal epithelial layers
2. The constant presence of saliva, which prevents the retention of the formulation in one area of the oral cavity leading to shorter contact time
3. Person to person variability caused by differences in tongue movements, saliva amounts, and saliva content
4. The limited surface area available for absorption
5. Ensuring patient comfort with a dosage form easy to spray and not causing any local reactions, discomfort, or erythema.

Formulation aspects of Oral sprays

The permeation of drugs across mucosal membranes also depends to an extent on the formulation factors. These will determine the amount and rate of drug released from the formulation, its solubility in saliva, and thus the concentration of drug in the tissues. In addition, the formulation can also influence the time the drug remains in contact with the mucosal membrane. After release from the formulation, the drug dissolves in the surrounding saliva, and then partitions into the membrane, thus the flux of drug permeation through the oral mucosa will depend on the concentration of the drug present in the saliva. This concentration can be manipulated by changing the

amount of drug in the formulation, its release rate, and its solubility in the saliva. The first two factors vary in different types of formulations, and the last can be influenced by changing the properties of the saliva that affect the solubility. Formulation of intra oral sprays depends upon application are available as fine mist or wet sprays. Fine mist aerosol generally expels fine stream of solution rather than micro-droplets from wet sprays.

An aerosol formulation consists of two essential components:

1. Product concentrate
2. Propellant.

Product concentrate:

The product concentrate consist of active ingredients, or a mixture of active ingredients and other necessary agents such as Penetration enhancers²⁹, solvents, antioxidants, flavoring agents, sweeteners, hydrophilic polymers, preservatives, acidifying agents, cosolvent²³ as shown in table 1 and table 2.

Penetration enhancers

Enhancers have been used to increase the permeation of drugs through the membrane, and thus increase the subsequent bioavailability. These should be pharmacologically inert and nontoxic, and should have reversible effects on the physicochemical properties of the oral mucosa. Penetration enhancers have different mechanisms of action depending on their physicochemical properties. Some examples of penetration enhancers and their mechanisms are bile salts (micellization and solubilization of epithelial lipids), fatty acids such as oleic acid (perturbation of intracellular lipids), azone (1-dodecylazacycloheptan-2-one) (increasing fluidity of intercellular lipids), and surfactants such as sodium lauryl sulfate (expansion of intracellular spaces).²⁹

Propellants:

The propellant provides the force that expels the product concentrate from the container and additionally is responsible for the delivery of the formulation in the proper form (i.e., spray, foam, semisolid). When the propellant is a liquefied gas or a mixture of liquefied gases, it can also serve as the solvent or vehicle for the product concentrate.²⁴

Ideal properties of propellants

1. It should be non toxic
2. It must be pure
3. It should be free from irritation effect.
4. It should have good solvent action on numbers of therapeutically active ingredients.
5. It should be chemically inert and non-reactive.
6. It should be non-flammable.

Types of propellants commonly used in pharmaceutical aerosols include chlorofluorocarbons, hydrocarbons, hydrochlorofluorocarbons and hydrofluorocarbons, and compressed gases. Different propellants used in oral aerosols are presented in Table 3 and table 4 represents marketed products.

Evaluation of oral sprays

Physiochemical test

1. Vapour pressure
2. Density
3. Moisture content
4. Identification of propellant
5. Concentrate: propellant ratio

Performance test

1. Leak test
2. Internal pressure testing
3. Delivery rate
4. Spray pattern
5. Net content
6. Dosage with metered valves

Stability testing

Toxicity study

Current research work carried on oral sprays:

An aerosol spray is one of the suitable alternatives to the solid dosage forms and can deliver the drug into the salivary fluid or onto the mucosal surface and thus is readily available for the absorption. As the spray delivers the dose in fine particulates or droplets, the lag time for the drug to be available for the site of the absorption is reduced. For example, a pharmacokinetic study of buccal insulin spray in patient with Type I diabetes revealed no statistical difference in glucose, insulin and C-peptide plasma level compared to insulin administered subcutaneously.³¹

One such spray called insulin buccal spray (IBS) was developed by Xu and co-workers with soybean lecithin and propanediol. Soybean lecithin has high affinity for biomembranes but does not enhance the transport of drugs due to low solubility. Propanediol can improve the solubility of soybean lecithin, and act as an enhancer. IBS was administered to diabetic rabbits; results indicated that insulin delivered through the buccal spray is an effective therapeutic alternative to the current medication system for treating diabetes.³² K. Bijoria and his co-workers evaluated the efficacy of isosorbide dinitrate buccal spray (Isomack) in attenuating the cardiovascular response to laryngoscopy and tracheal intubation in 60 patients undergoing elective surgery under general anesthesia. Patients were allocated to one of three groups of 20 patients each. Although significant tachycardia was present following intubation in all the three groups, the degree of tachycardia was greater in groups 2 and 3.³³

Bachmann and Gansser studied twenty patients angiographically before and after administration of glyceryl trinitrate (NTG) spray at a single oral dose of 0.8 mg in either a hydrosoluble (NTG-h) or liposoluble (NTG-I) solution. The assessment was by a randomized double-blind trial involving quantitative coronary angiography and pharmacologic stress testing using ergonovine maleate. The coronary angiography study demonstrates that the 2 different galenic formulations of NTG spray are equally efficacious in dilating the conductance coronary arteries under both conditions. When NTG-h and NTG-I oral spray were given subsequent to ergonovine-testing, Ergonovine-induced coronary vasoconstriction was released significantly for a period of at least 30 minutes. Both the NTG-h and NTG-I oral sprays are potent coronary vasodilators in patients with increased coronary vasomotor tone.³⁴

McInnes and co-workers evaluated Radiolabelled buprenorphine clearance from the buccal cavity and pharmacokinetic profiles of a sublingual spray formulation in the dog, to assist in interpretation of future pharmacokinetic studies. In a spray formulation (400 µg/100 µl in 30% ethanol) was administered sublingually to four beagle dogs, and in comparison, absorption of buprenorphine was relatively slow, with a T max of 0.56 ± 0.13 h. Good buccal absorption despite short residence time can be explained by lipophilicity of buprenorphine enabling rapid sequestration into the oral mucosa, prior to diffusion and absorption directly into systemic circulation.³⁷

Contox® is a formulation, which consists of three natural ingredients (Vit. E, evening primrose oil and ubiquinone Q10) using no artificial additive or solvent in order to increase solubilisation. The putative high bioavailability of Contox®3 was tested in humans. Data being derived in patients with myocardial insufficiency demonstrate a low

level of Q10 before use of oral mucosal administration. Following mucosal administration of the Q10 preparation via a spray the median plasma concentration of Q10 which was higher.³⁵

Patents on oral sprays

DUGGER III *et al.*, (2009) received U.S. Patent on Buccal, polar and non-polar spray containing zolpidem. Buccal aerosol sprays or capsules using polar and non-polar solvents were developed which provide zolpidem for rapid absorption through the oral mucosa, resulting in fast onset of effect. The buccal polar compositions comprise formulation I: aqueous polar solvent, zolpidem, and optional flavoring agent; formulation II: aqueous polar solvent, zolpidem, optionally flavoring agent, and propellant; formulation III: non-polar

solvent, zolpidem, and optional flavoring agent; formulation IV: non-polar solvent, zolpidem, optional flavoring agent, and propellant; formulation V: a mixture of a polar solvent and a non-polar solvent, zolpidem, and optional flavoring agent; formulation VI: a mixture of a polar solvent and a non-polar solvent, zolpidem, optional flavoring agent, and propellant.³⁸

Klokkers-Bethke, *et al.*, (2009) received U.S. Patent for a pharmaceutical aerosol spray for treating an angina attack of nitroglycerin. By spraying a dose a liquid spray composition of 0.1 to 2 weight percent of nitroglycerin, 2 to 60 weight percent of ethanol, 2 to 60 weight percent of propylene glycol, 10 to 50 weight percent of dichlorodifluoromethane and 30 to 70 weight percent of dichlorotetrafluoroethane into the buccal area of the mouth, a direct and rapid dispersion of a solution of the active agent over as large a portion as possible of the oral mucosa, which absorbs the active agent nitroglycerin was to be achieved. In this way, a large area was to be reached, thereby accelerating absorption of the active agent.⁴⁴

Blondino *et al.*, (2011) has got us patent on stable anti-nausea oral spray formulations and methods. Stable formulations of selective 5-hydroxytryptamine receptor antagonists for oral spray administration for absorption by the oral mucosa and related methods of preparation and administration are provided. A preferred composition includes ondansetron in a concentration of about 5.1 to about 5.2% w/w; propylene glycol in a concentration of about 60.1 to about 60.3% w/w; water in a concentration of about 5.3 to about 5.4% w/w; and ethanol in a concentration of about 27.1 to about 27.3% w/w. Additional preferred excipients are preservative free and/or non-aqueous or primarily non-aqueous.³⁹

Conclusion

The oral transmucosal route is gaining importance for systemic drug delivery because it does have significant advantages compared to the per oral route. The Intra oral spray technology offers formulation of many pharmacological agents making it preferred mode of delivery in diseases like angina, diabetes, and cardiovascular diseases. It allows more rapid absorption into the bloodstream than is possible with oral administration to the gastrointestinal tract. Oral spray administration is non-invasive, non technical and convenient for patients. In patients requiring rapid onset of action for therapeutic drugs, this route is more comfortable and convenient than intravenous drug administration, and costs may be significantly lower because no specialized care or equipments are necessary. In addition to the many potential advantages of oral transmucosal drug delivery, there are several

limitations that must be considered. Numerous drugs have been investigated for oral transmucosal delivery, yet few have become commercially available. Clinical need, and in many cases new indications, is often the driving force for developing an alternative drug delivery form. It thus belongs to an innovative class of oral delivery systems that have the potential, in the hope of providing a promising drug delivery system.

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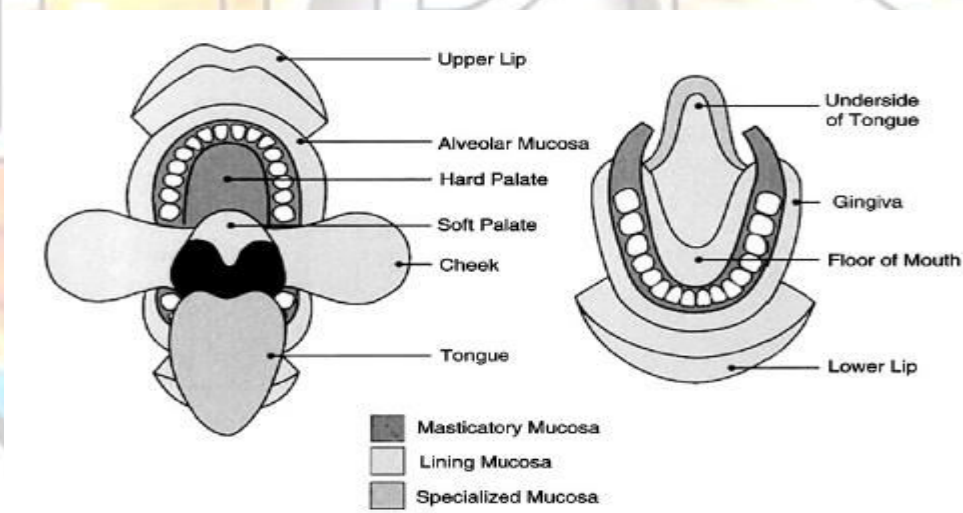


Fig. 1: Schematic representation of the different linings of mucosa in mouth

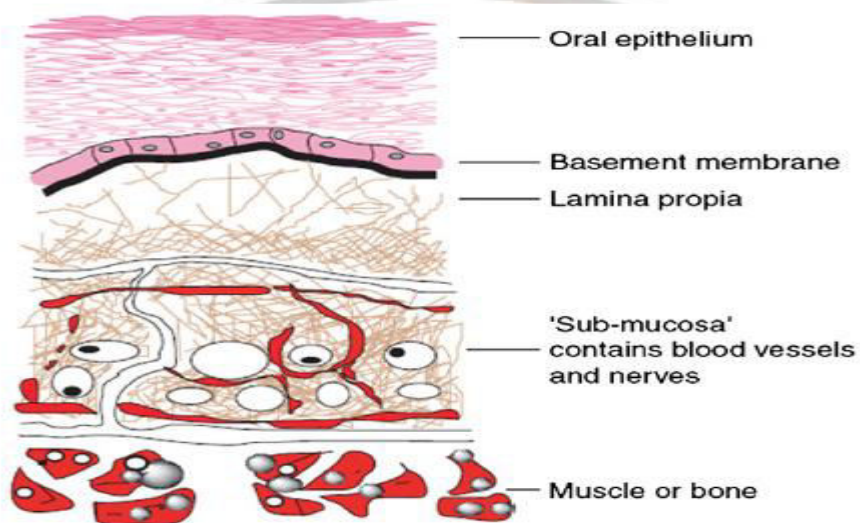


Fig. 2: Schematic diagram of buccal mucosa

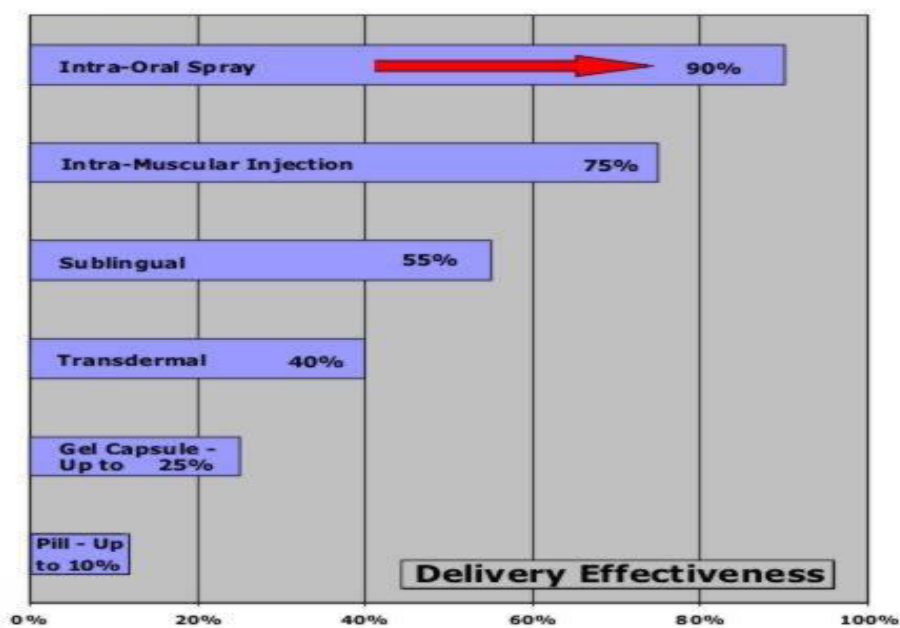


Fig 3: Absorption of vitamins via different routes

Table 1: Formulation of polar lingual sprays²⁴

Item	Examples
Active ingredients	cardiovascular agents, neuroleptics, cardiovascular agents, antidiabetic, analgesics, antihistergics, and drugs for erectile dysfunction, anti-migrain
solvents	Purified water, ethanol
Antioxidants	Ascorbic acid, Amino acids
Flavouring agent	Artificial fruits flavors
Sweeteners	Neotame, aspartame, mannitol, Sodium Saccharin
Preservatives	Phenol, benzoic acid, m-cresol, Methylparaben, Propylparaben, Sodium Benzoate, Cetylpyridinium Chloride
Buffers	Citrate, acetate and phosphate buffers, sodium chloride
Co-solvents	Propylene glycol, ethyl alcohol, glycerine, PEG, soya oil, PEG-60 Hydrogenated Castor Oil
*Hydrophilic polymer	Xanthan Gum, Sodium Carboxymethylcellulose

*used in formulation of artificial saliva sprays

Table 2: Formulation of Non-polar lingual sprays²⁴

Item	Examples
Active ingredients	cardiovascular agents, neuroleptics, cardiovascular agents, antidiabetic, analgesics, antihistergics, and drugs for erectile dysfunction, anti-migrain
solvents	Ethanol, butanol, P-11, P-12, P-114P-143A, P-227, olive oil, soya oil
Flavouring agent	Lemon oil

Table 3: Propellants used in oral formulation²⁴

Sr.No.	Propellant	Examples	No.
1	Chlorofluorocarbon (CFC)	Trichloromonofluoromethane Dichlorodifluoromethane Dichlorotetrafluoroethane	11 12 114
2	Hydrochlorofluorocarbons (HCFC) and Hydrofluorocarbons (HFC)	Trifluoromonofluoroethane Heptafluoropropane	134a 227

Table 4: Marketed oral sprays^(40,41,42,43,45,46,47,48,49)

Formulation	Generic name	Commercial name	Manufacturer or marketing company	Indication/description	Special technology or properties
Buccal Mist	Insulin mouth spray	Oral-lyn™ spray	Multiple international marketing companies	Treatment of Type I and Type II diabetes	RapidMist™ spray dose technology from Generex Biotechnology Corp.,
Sublingual Spray solution	Glyceryl trinitrate sublingual spray	Glytrin Spray®	Multiple, international companies e.g. Sano.-aventis, Surrey, UK; Ayrton Saunders Ltd., Wirral, UK; AFT Pharmaceuticals Ltd., Auckland, NZ	CFC free, Prevention and relief of angina attacks	Metered dose spray
Throat spray	Flurbiprofen throat spray	Benactiv®	Marketed in Italy by Reckitt Benckiser H.C. S.p.a.	Symptomatic treatment of inflammatory and postsurgical	

				oropharyngeal pain	
Mouth spray	Nicotine inhalation system	Nicotrol® Inhaler	Pharmacia and Upjohn, Pfizer, New York, NY, USA	Tobacco cessation	Despite the name this product delivers via the oral transmucosal route. Most of the nicotine is deposited in the mouth with less than 5% reaching the lower respiratory tract.
Lingual Spray	Zolpidem	Zolpimist	NovaDel	short-term treatment of insomnia	NovaMist™ delivery Technology
Sublingual	Isosorbide dinitrate Spray	Linitral spray			
Sublingual	Isosorbide dinitrate	Isocard spray		Treatment and prophylaxis of angina.	Metered dose aerosol.
sublingual spray	nitroglycerin sublingual spray	Nitromist	NovaDel	to treat or prevent attacks of chest pain (angina).	Nitromist
oral/buccal/sublingual/spray	nitroglycerin	Nitrolingual, Nitroquick, Nitrostat	W Lambert-P Davis-Pzer Pharmaceuticals	to treat or prevent attacks of chest pain (angina).	
Buccal spray	delta-9-tetrahydrocannabinol and cannabidiol	Sativex	GW Pharmaceuticals, PLC	AS adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis	
lingual spray	Sumatriptan oral spray		NovaDel	treatment of migraine headaches	New Drug Application (NDA) for this compound with the FDA in 2008.
Oral spray		Aqwet Spray	Cipla Limited	as a replacement for natural saliva	
Oral Spray	Cobroxin Oral Spray		XenaCare	Chronic Pain	
Throat Spray	Herbal Throat Spray		Kiwiherb	Sore or irritated throat Dry or hoarse throat Bad breath	Herbal product
Oral Spray	hyoscyamine Oral Spray		kaiserpermanente	used to treat stomach and bladder problems	
Buccal Spray		Oral-Recosulin	Shreya Life Sciences Pvt Ltd	for the treatment of type-1 and type-2 diabetes	collaboration with the US-based Genex Biotechnology Corporation
Oral spray		Nitrolingual pump spray	First Horizon Pharmaceutical corporation	For angina	