

oral spray – A review on promising drug delivery system for oral cavity

Abstract:

The oral mucosa has shown promising results for the systemic absorption of many drugs owing to the highly permeable nature of the mucosal membrane. It is also very attractive option for the local administration of drug into the oral cavity region. Oral sprays are very fast, the most effective and easy way to get daily dose vitamins, minerals, and other nutrients ingredients. The mouth spray design came out with aimed at improving patient compliance. Oral spray with Mucoadhesive polymers forms small droplets that quickly adheres to the mucosal surface and let the drug permeate into the blood circulation easily. Due to this advantage oral sprays have emerged as an effective alternative for bypassing extensive first pass effect. This review aims to compile information related to marketed oral spray preparation along with their formulation and clinical application.

Keywords: Oral mucosa, Oral spray, Mucoadhesive polymers, Vitamins, Buccal cavity

Introduction:

1. Overview of the buccal cavity:

1.1 Anatomic and Physiologic features

The oral mucosa presents a surface space of around 100 cm². Three unique types of oral mucosa are perceived: the masticatory mucosa, the covering mucosa and also the particular mucosa.

- ✓ The masticatory mucosa, addressing 25% of the whole oral mucosa, is 100–200 mm in thickness and covers the gingiva and also the hard sense of taste. it's firmly appended to the elemental constructions and is exposed to scraped area and shear pressure during rumination.
- ✓ The coating mucosa (60% of the whole oral mucosa) is 500–800 mm in thickness and

covers the lips, cheeks, delicate sense of taste, lower surface of the tongue and therefore the floor of the oral pit.

- ✓ The particular mucosa (15% of the whole oral mucosa) is found on the dorsum of the tongue and is related to taste.

The term 'buccal', irrespective of whether now and then, wrongly want to show the mucosa of the all-out oral fissure, alludes to the covering of the cheek and therefore the upper and lower lips, which address 33% of the entire oral mucosa surface [1,2]

Oral cavity membrane	structure	Surface area (cm ²)	Thickness (µm)	Blood Flow (ml.min ⁻¹ .cm ⁻²)
Buccal mucosa	Non- keratinized	50.2	500-800	2.40
Gingival mucosa	keratinized	-	200	1.47
Palatal	keratinized	20.1	250	0.89
Sublingual mucosa	Non- keratinized	26.5	100-200	0,97

Table 1: Surface area and thickness of oral cavity membranes [3]

1.2 Overview of Buccal drug delivery system:

Drugs are often delivered throughout oral mucosa into three distinct forms:

- a) Sublingual delivery of medications: the administration across the layer of the tongue's front surface and therefore the floor of mouth.
- b) Buccal supply: composed primarily of the liner of the cheeks and therefore the BM membrane.
- c) Local delivery of drugs: consisted of administration, all told places other than those 2 previous zones.

These sites are bodily different in their drug penetration, delivery rate and ability to sustain a delivery mechanism for a particular fundamental measure to release drugs out of the supplies and into the mucosa. [3]

1.3 Advantages of buccal drug delivery systems:

- Excellent accessibility.
- Presence of smooth muscle and relatively immobile mucosa, hence suitable for

administration of retentive dosage forms

- Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability
- Low enzymatic activity
- Suitability for drugs or excipients that mildly and reversibly damages or irritates the mucosa
- Painless administration
- Easy drug withdrawal
- Facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation
- Versatility in designing as multidirectional or unidirectional release systems for local or systemic actions etc.^[3]

Formulation	Active constituent	Brand name	Manufacturer or marketing company	Application	Special technology or properties
Buccal Mist ^[5]	Insulin	Oral-Lyn™ spray	Multiple international marketing companies	Treatment of Type I and Type II diabetes	Rapid Mist™ spray dose technology from Genex Biotechnology Corp.
oral/buccal/sublingual/spray ^[6]	nitroglycerin	Nitrolingual, Nitroquick, Nitrostat	W Lambert-P Davis-P.zer Pharmaceuticals	to treat or prevent chest pain attacks (angina).	-
Buccal spray ^[7]	delta-9-tetrahydrocannabinol and cannabidiol	Sativex	GW Pharmaceuticals, PLC	As a supplemental treatment for the symptomatic	

				relief of neuropathic pain in multiple sclerosis	
Buccal Spray	recosulin	Oral-Recosulin	Shreya Life Sciences Pvt Ltd	for the treatment of type-1 and type-2 diabetes	Collaboration with Generex Biotechnology Corporation, based in the United States
Mouth spray ^[8]	Nicotine inhalation system	Nicotrol ® Inhaler	Pharmacia and Upjohn, Pfizer, New York, NY, USA	Tobacco cessation	Despite its name, this product is administered through the oral mucosal route. The majority of nicotine is deposited in the mouth, with only about 5% reaching the lower respiratory tract.
Oral spray ^[9,10]	-	Aqwet Spray	Cipla Limited	as a substitute for natural saliva	-
Oral Spray ^[11]	Cobroxin Oral Spray	-	XenaCare	Chronic Pain	-
Oral Spray ^[12]	hyoscyamine Oral Spray	-	kaiserpermanente	used to treat problems & stomach and bladder	-
Oral spray ^[13]	Nitroglycerine	Nitrilingual pump spray	First Horizon Pharmaceutical corporation	For angina	-

Throat spray ^[14,15]	Flurbiprofen throat spray	Benactivin®	Marketed in Italy by Reckitt Benckiser S.p.a.	Symptomatic treatment of inflammatory Postsurgical oropharyngeal pain	-
Throat Spray ^[16]	Herbal Throat Spray	-	Kiwi herb	Sore or irritated throat Dry or hoarse throat Bad breath	Herbal product
Sublingual solution Spray ^[17]	Glyceryl trinitrate sublingual spray	Glytrin Spray®	Multiple, international companies e.g. Sano. Aventis, Surry, UK; Ayrton Saunders Ltd., Wirral, UK; AFT Pharmaceuticals Ltd., Auckland, NZ	CFC free, Prevention and relief of angina attacks	Metered dose spray
Lingual Spray ^[18]	Zolpidem	Zolpimist	NovaDel	short-term treatment of insomnia	Nova Mist™ delivery Technology
Sublingual ^[19]	Isosorbide dinitrate	Isocard spray	NovaDel	Treatment and prophylaxis of angina.	Metered dose aerosol.

sublingual spray	nitroglycerin sublingual spray	Nitromist	NovaDel	to treat or prevent attacks of chest pain (angina).	Nitro mist
lingual spray ^[20]	Sumatriptan oral spray	-	NovaDel	treatment of migraine headaches	New Drug Application (NDA) for this compound with the FDA in 2008.

Table 2: various marketed oral spray preparations

2. Marketed Oral Spray Formulations:

2.1 The RapidMist™ System for Buccal Delivery of Insulin:

Generex Oral-lyn™ (buccal insulin, Oralin) may be a liquid formulation of short acting insulin that's administered using Generex's metered dosage aerosol applicator (RapidMist™). Generex Oral-lyn™ is sprayed into the buccal cavity, where the insulin is absorbed into the bloodstream through the mucosal lining. Generex Oral-lyn™ is probably going to be used as both an add-on to current long-acting insulin treatment and a substitute for injectable short acting insulin. If licensed, it should replace the requirement for injectable insulin throughout the day, requiring injections just for overnight insulin maintenance in patients with type 1 disease and for several with type 2 disease. Dosage is love current short-acting insulin. The formulation is stored for up to three months at temperature if more than 15 months are left before product expiry. Generex Oral-lyn™ is that the first insulin agonist to be administered and absorbed through the buccal mucosa. Early trials suggest that the formulation is quickly absorbed within the mouth with a more rapid onset of action than subcutaneous injected insulin. Generex Oral-lyn™ may reduce the quantity of required injections, improving compliance, quality of life and reducing needle stick hazards. ^[5]

2.2 Nitroglycerin (NTG) oral spray:

NTG oral spray (Nitrolingual) – nitroglycerin in aromatized oily solution is enclosed in an aerosol container that holds 10 ml of solution, enough for about 200 doses of 0.4 mg NTG each. The drug is administered onto the oral mucosa preferably the tongue - without inhaling. During application, the sprayer is kept vertical with the nozzle head pointing upward and as near the

mouth as possible. Each spray lasts about 200 msec Oral NTG spray in four patients' cardiovascular systems and exercise-induced angina pectoris When compared to a placebo spray, this new version of the NTG app significantly increased treadmill activity and pre-angina onset. Greater improvement during exercise (31%) in our patients is associated with the beneficial effect of less NTG language expressed by others. Blood pressure decreases in both the sitting and standing positions, with an increase in heart rate in the standing position, following subconscious NTG, indicating absorption and pharmacologic activity of the drug in spray form. The hemodynamic effects became apparent almost immediately (" less than "2 minutes).^[6]

2.3 Delta-9-Tetrahydrocannabinol/Cannabidiol Oromucosal Spray (Sativex):

Delta-9-tetrahydrocannabinol (THC) / cannabidiol (CBD) oromucosal spray (THC / CBD, Sativex, nabiximols) is available in many countries for the treatment of multiple sclerosis (MS), which is associated with moderate to severe stiffness in patients undergoing it despite not responding well to other anti-respiratory drugs, and demonstrates significant clinical improvement in spasticity-related A significant phase 3 trial discovered that 12 weeks of THC/CBD treatment improved MS-related spasticity in patients who had previously failed to respond to other anti-spasticity agents. The development of spasticity was prolonged with THC/CBD without evidence of dose tolerance, and real-world studies confirm the efficacy of THC/CBD in daily clinical activities. THC / CBD influenced the development of both health-related and daily living activities. THC/CBD is generally well tolerated; however, as the THC/CBD dose is increased, side effects such as dizziness may occur. THC / CBD has a low risk of side effects and psychological consequences. To summarise, THC/CBD oromucosal spray is an alternative treatment for MS-related spasticity that is not completely relieved by current anti-inflammatory medication.^[7]

2.4 Oral- Recosulin:

The DNA human buccal insulin spray, which was created using Genex Biotechnology's RapidMist technology for insulin delivery, is effective in treating type 1 and type 2 diabetes. The main benefit of this insulin spray is that diabetic patients will no longer need to inject insulin. Without it, the spray is immediately effective and provides a very high pharmacodynamic profile with no pain when ingested by patients.

2.5 Nicotrol® Inhaler:

These therapies are thought to be most effective when used to inject nicotine (e.g., NRT) or

when used sparingly to stimulate or prevent nicotine effects in the brain (e.g., varenicline or bupropion), thereby reducing withdrawal symptoms experienced while smoking. Although effective pharmacotherapy is critical for successfully controlling nicotine addiction, improved formulation and the introduction of new drugs may improve the treatment effect of various tobacco addiction-related disorders. The proposed method of drug delivery to the lungs is expected to improve nicotine addiction treatment with minimal side effects in the coming years. However, there is insufficient data to conclude the current market based on the effectiveness of various agents. Choosing an effective operation Each patient should be assigned a different agent. Patient preferences, medication adherence issues, prior knowledge and withdrawal agents, and patient characteristics such as contraindications, depression history, and smoking rate are all important considerations. Finally, pharmacotherapy should be accompanied by appropriate ethical advice to improve long-term end-of-life levels. ^[8]

2.6 Aqwet oral Spray:

New synthetic saliva formulations with varying concentrations of SCMC, MC, and HPMC have been created. Each composition exhibits a high level of quality. This is clear from the description of appearance and body structures, where all of the ingredients were discovered to be chemically and physically compatible. Because of the use of cellulose and albumin extracts in these structures, the true characteristics of these new salivary glands are closely related. The entire structure's pH is within the normal range of human saliva. The addition of orange flavor and dextrose improves the flavor of the composition. The addition of electrolytes that mimic those found in natural saliva, as well as fluoride as a preservative, can help to maintain dental integrity while also increasing the clinical effectiveness of these preparations. ^[9,10]

2.7 Carboxin oral spray:

Carboxin is the active ingredient in this product, and the inactive ingredients are Citric Acid, Methyl Paraben, Natural Flavoring, and Pure Water. Cobroxin is an oral medication used to treat headaches, neck pain, shoulder pain, cramps, back pain, and neuralgia. It also includes a topical gel for treating joint pain caused by recurring depression and arthritis. According to XenaCare, Cobroxin is the first OTC pain reliever that has been clinically proven to treat chronic moderate to severe pain (Stage 2), whereas many other Phase 2 drugs require instructions, such as Tylenol 3, Percocet, and Vicodin. ^[11]

2.8 Hyoscyamine Sulfate Oral spray:

Oral spray Hyoscyamine Sulfate contains 0.125 mg Hyoscyamine Sulfate per mL and 5 percent v/v oral alcohol. Alcohol, FD&C red # 40, FD&C yellow # 6, flavor, glycerin, pure water, benzoic acid, sodium citrate, sorbitol solution, and sucrose are all inactive ingredients. Oral administration of Hyoscyamine Sulfate results in complete absorption. Hyoscyamine Sulfate quickly leaves the bloodstream and spreads throughout the body after ingestion. Hyoscyamine Sulfate has a half-life of 2 to 3 1/2 hours. Although tropic acid and tropine are partially hydrolyzed by hyoscyamine sulphate, the majority of the drug is excreted unchanged in the urine within the first 12 hours. Breast milk contains only trace amounts of this drug. The blood-brain barrier and the placental barrier are both crossed by hyoscyamine sulphate. Hyoscyamine Sulfate is useful as an adjunct therapy in the treatment of peptic ulcers. It can also be used to treat diarrhea, visceral spasm, and hypermotility in spastic colitis, cystitis, pylorospasm, and associated abdominal cramps. It may be used to treat symptoms associated with functional bowel disorders such as mild dysentery, diverticulitis, and dangerous enter colitis. ^[12]

2.9 Nitrolingual® Pumpspray:

Lingual spray, 400 mcg per spray, available in 60 or 200 metered sprays per container. Nitro lingual Pump spray is a nitrate vasodilator indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease. At the onset of an attack, administer onto or under the tongue. Repeat every 5 minutes as needed. Do up to three metered sprays within a 15-minute period. If chest pain persists, advise prompt medical attention May be used prophylactically 5 to 10 minutes prior to engaging in activities that might precipitate an acute attack. Nitroglycerin is quickly absorbed by the tongue and surrounding mucous membranes and has an immediate therapeutic effect. It is best to use Nitrolingual®Pumpspray while sitting. ^[13]

2.10 Flurbiprofen throat spray:

Flurbiprofen 8.75mg spray is well tolerated, provides fast and long lasting relief for sore throat and is suitable for using p.r.n (as needed) during a sore throat episode. Flurbiprofen 8.75mg spray can be recommended for the symptomatic treatment of sore throat, while antibiotics should be reserved for patients who are severely ill or at increased risk of complications. Flurbiprofen 8.75 mg, in the form of a spray or a lozenge, effectively relieves the pain of a sore throat caused by a URTI. In comparison to lozenges construction, less spray was developed, and both designs outperformed safety profiles. Depending on the patient's preference, the spray and lozenge formulations provide two distinct treatment options for relieving sore throat symptoms. ^[14,15]

2.11 Herbal Throat Spray:

Herbal Throat Spray is a delectable new oral health solution. A one-of-a-kind blend that includes the traditional New Zealand Kawakawa (*Macropiper excelsum*), which is known for its delicious pepper flavor and long history of use in traditional Maori medicine. In addition to Manuka Honey, it contains certified organic Thyme, Echinacea root, and Propolis.

- Organic herbal ingredients
- Refreshing natural flavor
- Easy spray
- Cleanses the mouth
- Aids in the elimination of germs that cause bad breath ^[16]

2.12 Glyceryl Trinitrate spray:

The active ingredient in each spray is 400 micrograms glyceryl trinitrate. Ethanol and propylene glycol are also present, as is a non-particle solution in a CFC-free pump. Glyceryl Trinitrate spray relaxes smooth muscles. Because the walls of most arteries and veins are made of smooth muscle, glyceryl trinitrate aids in the expansion of these vessels. When you inhale Glyceryl Trinitrate, the spray under your tongue enters your bloodstream quickly. The action of Glyceryl Trinitrate spray promotes faster and easier blood flow. This means your heart doesn't have to work as hard. High blood flow to the heart also indicates that the heart is working more efficiently. Glyceryl trinitrate's actions provide relief from angina attacks and may help to prevent future attacks. Glyceryl Trinitrate spray is used to treat and prevent the onset of angina (chest pain). A meter dosage valve and a protective cap are included with the aluminum canister. Each 10g solution container is designed to deliver at least 180 volumes. Colorless or nearly colorless, clear, non-residual solution. ^[17]

2.13 Zolpimist (zolpidem tartrate) Oral Spray:

Zolpimist (zolpidem tartrate) Oral Spray is used to treat short-term insomnia caused by difficulty falling asleep. In controlled clinical studies, zolpidem tartrate was shown to reduce sleep delays by up to 35 days. Clinical trials to prove efficacy lasted 4–5 weeks, with a formal sleep test at the conclusion of treatment. Zolpimist is available as a clear, colorless, cherry solution that is intended to be sprayed directly on the tongue. At 100 L, a 1 meter (single spray) actuation of Zolpimist delivers 5 mg of zolpidem tartrate. Ten milligrams of zolpidem tartrate are delivered by two actuators. After the first five operations, each child-resistant container has 60 mers of

actuation. The total amount of available volumes is determined by the number of actuations per unit (1 or 2) and the frequency of initiation.^[18]

2.13.1 Mechanism of Action:

The active ingredient in zolpidem tartrate, zolpidem, is a sedative with a chemical structure that is unrelated to benzodiazepines, barbiturates, or other addictive drugs. It interacts with the GABA-BZ receptor complex and has some of the same pharmacological properties as benzodiazepines. Unlike benzodiazepines, which do not bind indiscriminately and activate all types of BZ receptors, zolpidem binds to the BZ1 receptor in vitro with a high compliance number of small units 1 / 5. Although the selective binding of zolpidem to the BZ1 receptor is inconclusive, it could explain the lack of myorelaxant and anticonvulsant effects in animal studies, as well as deep sleep retention (stages 3 and 4) in human studies of hypnotic doses of zolpidem. Zolpidem is primarily excreted in the kidney as inactive metabolites. The binding amount of zolpidem protein was found to be 92.5 0.1 percent and remained constant across concentrations ranging from 40 to 790 ng/mL. After a two-week night dose of 20 mg zolpidem tartrate, zolpidem did not accumulate in young adults. The pharmacokinetics of Zolpimist 10 mg were compared in a crossover study of 14 healthy young men (18-45 years old) when given during fasting for at least 8 hours or 5 minutes after eating a high-fat diet. These findings suggest that Zolpimist, like all zolpidem products, should not be taken right before or right after a meal to promote sleep onset.

2.14 Isosorbide dinitrate (ISDN) spray:

The effects of isosorbide dinitrate (ISDN) spray (Eye Mack Spray) on central hemodynamics were compared to sublingual glyceryl trinitrate (nitroglycerin) and ISDN, with a focus on the onset and duration of action of ISDN. ISDN spray (2, 2.5 mg), glyceryl trinitrate (TNG, 0.3 mg), and standard ISDN tablet (5 mg) were given in a single blind crossover form to nine patients with acute myocardial infarction. Swan- Ganz catheter is used to monitor hemodynamics. Every minute for 10 minutes, every 5 minutes for the next 20 minutes, and then every 15 to 30 minutes to 120 minutes, systolic pulmonary artery pressure (s-PA), systolic pressure (s-BP), and heart rate are measured. The onset and duration of action, as well as the magnitude of change, were compared between the three drugs using s-PA as a measure of nitrate action. The ISDN spray had a faster onset of action (2.67 +/- 2.4 min, meaning +/- SD) than TNG (2.67 +/- 1.00 min), as well as a longer operating time (57.4 +/- 42.1 min), which was significantly longer than TNG

(11.4 +/- 6.4 min, p less than 0.05). ISDN spray (2.5 mg) caused hemodynamic changes similar to those caused by 0.3 mg TNG or 5 mg ISDN. The findings of this study led us to believe that ISDN spray is an effective agent for preventing angina attacks with its rapid onset and long-term efficacy.^[19]

2.15 Nitro lingual Pump spray:

Nitro lingual Pump spray is a nitrate vasodilator that has been shown to be very effective in relieving or stopping angina pectoris because of coronary artery disorder. Tongue spray, four hundred mcg in line with spray, is to be had at 60 or 2 hundred meters spray in keeping with box. Nitroglycerin causes an increase in guanosine three', five'-monophosphate (cyclic GMP) in smooth muscle and other tissues by releasing the free radical nitric oxide (NO), which activates guanylate cyclase. This results in dephosphorylation of minor myosin chains, which alters clean muscle contraction and causes vasodilation.

2.16 Sumatriptan oral spray:

Sumatriptan can be absorbed orally, that the preliminary pharmacokinetics of Lingual Spray is almost identical to that once the injection of sumatriptan, and that this primary pharmacokinetic substance turned into regular with proof of on the spot movement in patients with 50-mg low-dose tablets. further, the formation of LS has been properly tolerated. these initial research assist the continuous development of this new shape and a new control technique.^[20]

3. Conclusion:

It has been a very well known fact that the oral route of administration is the most popular route of drug administration. However the drawbacks like extensive first pass metabolism and drug degradation in stomach makes this route not suitable for all drugs and thus an alternative oral drug delivery systems are necessary to exploit benefits of oral route. There are many oral spray preparations approved by various regulatory agencies throughout the globe which allow drugs to enter to the systemic circulation via the oral mucosal membrane. These oral sprays also improve the permeability of drug across mucosal membrane by improving the residence time i.e. in situ gel forming oral spray. Many researchers are working to develop oral spray formulations for drugs which need quick permeation followed by quick onset of action and also provide an effective alternative of conventional oral drug delivery systems.

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