



Oral Spray – A Review on Promising Drug Delivery System for Oral Cavity

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Aim: This review aims to compile information related to marketed oral spray preparation along with their formulation and clinical application.

Objective: The main objective of this overview is to study the marketed oral spray dosage form for treatment of different diseases and learn about its advantages over the other oral dosage forms e.g. tablet, capsule, patches etc.

Description: 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. The oral mucosa has shown promising results for the systemic absorption of many drugs owing to the highly permeable nature of the mucosal membrane. Oral sprays are very fast, the most effective and easy way to get daily dose vitamins, minerals, and other nutrients ingredients. Due to this advantage oral sprays have emerged as an effective alternative for bypassing extensive first pass effect.

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. 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.

Keywords: Oral mucosa; oral spray; mucoadhesive polymers; vitamins; buccal cavity.

1. INTRODUCTION

1.1 Overview of the Buccal Cavity

1.1.1 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].

1.1.2 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 [3-5].

1.1.3 Advantages of oral spray over the other dosage form drug delivery systems

- 1) The oral method of delivery is also very helpful for individuals who have trouble swallowing pills or capsules and it is cost effective because a smaller dosage is required.
- 2) It's possible that faster absorption will result in a rapid commencement of effect.
- 3) Patient compliance for disabled bedridden patients, as well as for travellers and busy people without ready access to water.
- 4) Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability
- 5) Low enzymatic activity
- 6) Suitability for drugs or excipients that mildly and reversibly damages or irritates the mucosa
- 7) Painless administration
- 8) Easy drug withdrawal
- 9) Facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation
- 10) Versatility in designing as multidirectional or unidirectional release systems for local or systemic actions etc [3].

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

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 2. Various marketed oral spray preparations

Formulation	Active constituent	Brand name	Manufacturer or marketing company	Application	Special technology or properties
Buccal Mist[6]	Insulin	Oral-Lyn™ spray	Multiple international marketing companies	Treatment of Type I and Type II diabetes	Rapid Mist™ spray dose technology from Generex Biotechnology Corp.
oral/buccal/sublingual /spray[7]	Nitroglycerin	Nitro lingual, Nitro quick, Nitrostat	WLambert–P Davis–P.zer Pharmaceuticals	to treat or prevent chest pain attacks (angina).	-
Buccal spray[8]	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[9]	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[10]	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[11]	-	Aqwet Spray	Cipla Limited	as a substitute for natural saliva	-
Oral Spray[12]	Cobroxin Oral Spray	-	XenaCare	Chronic Pain	-
Oral Spray[13]	hyoscyamine Oral Spray	-	kaiserpermanente	used to treat problems & stomach and bladder	-
Oral spray[14]	Nitroglycerine	Nitrilingual pump spray	First Horizon Pharmaceutical corporation	For angina	-
Throat spray[15]	Flurbiprofen throat spray	Benactiv®	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[20]	nitroglycerin sublingual spray	Nitromist	NovaDel	to treat or prevent attacks of chest pain (angina).	Nitro mist
lingual spray[21]	Sumatriptan oral spray	-	NovaDel	treatment of migraine headaches	New Drug Application (NDA) for this compound with the FDA in 2008.

2. MARKETED ORAL SPRAY FORMULATIONS

2.1 The RapidMist™ System for Buccal Delivery of Insulin

Generex Oral-lyn™ (buccal insulin, Oralin) is a liquid formulation of short-acting insulin that is delivered via Generex's RapidMist™ metered dosage aerosol applicator. The insulin in Generex Oral-lyn™ is sprayed into the buccal cavity and absorbed into the bloodstream via the mucosal lining.

Generex Oral-lyn™ will most likely be used as a supplement to current long-acting insulin therapy as well as a replacement for injectable short-acting insulin. If approved, it could eliminate the need for injectable insulin throughout the day, leaving only overnight insulin maintenance injections for patients with type 1 diabetes and a few patients with type 2 diabetes. The dosage is the same as with current short-acting insulin. If there are more than 15 months until the product expires, the formulation can be kept at room temperature for up to three months. The first insulin agonist to be administered and absorbed through the buccal mucosa is Generex Oral-lyn™. Preliminary studies suggest that the formulation accumulates quickly in the mouth and has a faster onset of action than subcutaneously injected insulin. Generex Oral-lyn™ may reduce the number of injections needed, improving compliance and well being while also reducing needle stick challenges [6].

2.2 Nitroglycerin (NTG) Oral Spray

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. Without inhaling, the drug is applied to the oral mucosa, preferably the tongue. The sprayer should be kept vertical during application, with the nozzle head pointing upward and as close to 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. The beneficial effect of less NTG language expressed by others is associated with greater improvement during exercise (31 percent) in our patients. Following subconscious NTG, blood pressure drops in both

sitting and standing positions, with a rise in heart rate in the standing position, indicating absorption and pharmacologic activity of the drug in spray form. The hemodynamic effects were immediately noticeable ("less than "2 minutes) [7].

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 [8].

2.4 Oral-Recosulin

The DNA human buccal insulin spray, which was created using Generex 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 [9].

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 [10].

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 pH of the entire structure is within the range of human saliva. The flavour of the composition is improved by the addition of orange flavour and dextrose. Electrolytes that mimic natural saliva, as well as fluoride as a preservative, can help to maintain dental integrity while also improving the clinical effectiveness of these preparations [11].

2.7 Carboxin Oral Spray

Citric Acid, Methyl Paraben, Natural Flavoring, and Pure Water are the inactive ingredients in this product, while Carboxin is the active ingredient. Headaches, neck pain, shoulder pain, cramps, back pain, and neuralgia are all treated with cobroxin, an oral medication. A topical gel for treating joint pain caused by recurring depression and arthritis is also included. Cobroxin is the first OTC pain reliever that has been clinically proven to treat chronic moderate to severe pain (Stage 2), according to XenaCare,

whereas many other Phase 2 drugs, such as Tylenol 3, Percocet, and Vicodin, require instructions [12].

2.8 Hyoscyamine Sulfate Oral spray

Hyoscyamine Sulfate oral spray contains 0.125 mg of Hyoscyamine Sulfate per mL and 5% v/v oral alcohol. Inactive ingredients include alcohol, FD&C red # 40, FD&C yellow # 6, flavour, glycerin, pure water, benzoic acid, sodium citrate, sorbitol solution, and sucrose. 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 medication is eliminated in the urine within the first 12 hours. Breast milk contains only trace amounts of this drug. Hyoscyamine sulphate can pass through the blood-brain barrier and the placental barrier. Peptic ulcers can be treated with Hyoscyamine Sulfate as an adjunct therapy. In spastic colitis, cystitis, pylorospasm, and associated abdominal cramps, it can also be used to treat diarrhoea, visceral spasm, and hypermotility. It could be used to treat symptoms of functional bowel disorders like mild dysentery, diverticulitis, or dangerous enter colitis [13].

2.9 Nitrolingual® Pumpspray

Lingual spray, 400 micrograms per spray, 60 or 200 metered sprays per container. Nitro lingual Pump spray is a nitrate vasodilator that is used to treat or prevent angina pectoris caused by coronary artery disease. Administer onto or under the tongue at the first sign of an attack. As needed, repeat every 5 minutes. Within a 15-minute period, spray up to three times with a metered sprayer. If chest pain occurs, seek immediate medical attention Utilize 5 to 10 minutes before engaging in activities that could trigger an acute attack as a preventative measure. Nitroglycerin is rapidly absorbed by the tongue and surrounding mucous membranes, providing immediate relief. When using Nitrolingual®Pumpspray, it is best to do so while sitting [14].

2.10 Flurbiprofen Throat Spray

Flurbiprofen 8.75mg spray is well tolerated, will provide rapid and long-lasting sore throat relief,

which can be used 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 must be reserved for patients who are severely ill or at higher 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 [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 meres 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].

2.14 Mechanism of Action

Zolpidem tartrate's active ingredient, zolpidem, is a sedative with a chemical structure unrelated to benzodiazepines, barbiturates, or other addictive drugs. It has some of the same pharmacological properties as benzodiazepines and interacts with the GABA-BZ receptor complex. In vitro, zolpidem binds to the BZ1 receptor with a high compliance number of small units 1 / 5, unlike benzodiazepines, which do not bind indiscriminately and activate all types of BZ receptors. Although evidence for zolpidem's selective binding to the BZ1 receptor is lacking, 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 the drug. Inactive metabolites of zolpidem are primarily excreted in the kidney. The binding amount of zolpidem protein was determined to be 92.5 0.1 percent and was consistent across concentrations of 40 to 790 ng/mL. In young adults, zolpidem did not accumulate after a two-week night dose of 20 mg zolpidem tartrate. In a crossover study of 14 healthy young men (18-45 years old), the pharmacokinetics of Zolpimist 10 mg were compared when given during fasting for at least 8 hours or 5 minutes after eating a high-fat diet. To promote sleep onset, Zolpimist, like all zolpidem products, should not be taken right

before or right after a meal, according to some conclusions.

2.15 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 the onset and duration of ISDN's action being the most important factors. In a single blind crossover study, nine patients with acute myocardial infarction were given ISDN spray (2, 2.5 mg), glyceryl trinitrate (TNG, 0.3 mg), and standard ISDN tablet (5 mg). A 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 significantly longer operating time (57.4 +/- 42.1 min, p less than 0.05) than TNG (11.4 +/- 6.4 min), as well as a faster onset of action (2.67 +/- 2.4 min, meaning +/- SD) than TNG (2.67 +/- 1.00 min). ISDN spray (2.5 mg) caused hemodynamic changes that were 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 because of its rapid onset and long-term efficacy [19].

2.16 Nitro lingual Pump spray

Nitro lingual Pump spray is a nitrate vasodilator that has been shown to relieve or stop angina pectoris caused by coronary artery disease. Tongue spray, 400 mcg in accordance with spray, is available at 60 or 2 hundred metres spray in accordance with the box. By releasing the free radical nitric oxide (NO), which activates guanylate cyclase, nitroglycerin causes an increase in guanosine three', five'-monophosphate (cyclic GMP) in smooth muscle and other tissues. Dephosphorylation of minor myosin chains occurs as a result, altering clean muscle contraction and causing vasodilation [20].

2.17 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 [21].

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 explain 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 improves the permeability of drug across mucosal membrane by improving the residence time i.e. insitu 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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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