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A Review on Novel Drug Delivery System

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Abstract

Oral spray forms small droplets that quickly adsorb to the mucosal surface and allow the drug permeate into the blood circulation easily. The oral mucosa has shown encouraging results for the systemic absorption of many drugs due to the high permeability 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 these advantage oral sprays is seemed as an effective alternative of other oral medications as it bypassing the extensive first pass metabolism.

It has been a very well-known fact that the oral route of administration is the most popular way 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 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: Blood circulation; Oral mucosa; Vitamins; Minerals

Introduction

Medication distribution across the oral mucous membrane is seen to offer a promising alternative to traditional oral medication delivery techniques. The medicine is absorbed directly through the mucosal lining of the mouth under the tongue, which is highly rich in vascular blood supply, in the oral spray dose form. When a faster start of action is sought with higher patient compliance than orally taken medication, oral spray is effective. The oral cavity is more permeable than the vocal cavity in terms of permeability. For a speedier commencement of activity, the oral spray should be sprayed. Dose homogeneity of oral spray is a technical problem in terms of formulation. Spray, on the other hand, is easier to administer than other oral medications [1].

The key benefits of oral spray are the elimination of the first pass effect, quick medication absorption, great efficacy, a large surface area for absorption and numerous other benefits. In this distribution method, the medicine enters the arterial circulation *via* the oral vein and capillaries, then the jugular vein and finally the superior vena cava. The oral mucosa is quite vascular. Drugs ingested through the oral mucosa enter the systemic circulation directly, bypassing the GI tract and first-pass metabolism in the liver. For certain medications, this effect results in a faster beginning of action *via* a more comfortable and easy delivery route than the intravenous approach [2].

Literature Review

Overview of buccal cavity and absorption mechanism

Anatomic and physiologic features: The oral mucosa presents a surface space of around 100 cm^2. Three unique types of oral mucosa are apparent: The masticatory mucosa, the covering mucosa and also the particular mucosa (Table 1).

Table 1: Overview of buccal cavity and absorption mechanism.

Mucosa	Characteristics
The masticatory mucosa	Involving 25% of the whole oral mucosa. It is 100 mm-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	Involving 60% of the whole oral mucosa. It is 500 mm-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	Involving 15% of the whole oral mucosa. It is found on the dorsum of the tongue and is related to taste

Overview of buccal drug delivery system

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

Sublingual delivery of medications: The administration across the layer of the tongue's front surface and therefore the floor of mouth.

Buccal supply: Composed primarily of the liner of the cheeks and therefore the BM membrane.

Local delivery of drugs: Consisted of administration, all oral places other than above two previous zones.

Mechanism of oral absorption

The permeability of the solution, ionisation and molecular weight of substances all play essential roles in determining the absorption capacity of the oral mucosa. When the pH of the carrier is low (more acidic), the absorption of various medications through the oral mucosa rises, while it decreases when the pH is high (more alkaline). Endocytosis (the ingestion of particles by a cell as if by hollowly wrapping itself around it) is also capable of absorption by cells of the oral epithelium and epidermis. The particles absorbed are usually too big to diffuse through its wall). This method is unlikely to be utilised throughout the stratified epithelium.

Active transport pathways within the oral mucosa are also implausible. However, it is thought that acidic stimulation of the salivary glands, together with vasodilation, aids in absorption and uptake into the circulatory system. The mucous membrane that lines the mouth is coated by squamous epithelium and contains mucous glands. Oral mucosal tissue is comparable to buccal mucosal tissue. The salivary glands are made up of lobules of cells that produce saliva into the mouth *via* the salivary ducts. The parotid, submandibular and oral salivary glands are the three pairs of salivary glands located on the floor of the mouth. The more acidic the flavour, the more salivary secretion is stimulated [3].

The oral artery travels forward to the oral gland, where it nourishes the gland as well as branches to the surrounding muscles and mucous membranes of the mouth, tongue and gums. Two symmetrical branches meet and connect at the tip of the tongue behind the jawbone.

Another branch connects and anastomoses with the facial artery's submental branches. The oral artery is derived from the lingual artery, which is the body's main blood supply to the tongue and the floor of the mouth and is derived from the external carotid artery. The proximity to the internal carotid artery enables for quick access to its path, which supplies the majority of the cerebral hemisphere.

Discussion

Oral glands

Salivary glands are found on the floor of the mouth, beneath the tongue and are known as oral glands. Because of the abundant blood supply and high permeability, drugs with infrequent dosage regimens and short delivery times might be successfully administered orally. The oral route has a quick onset of action. Oral glands are well recognised for their lubricating and binding properties. Secretion from the oral glands makes food slick and easy to swallow.

Saliva secretion plays a major role in shaping the principle physiological environment of the oral cavity in terms of pH, composition and fluid volume. It acts as a protective fluid in all oral cavity tissues, hydrates oral mucosal dosage forms and promotes the mineralization and demineralization of tooth enamel. Saliva secretion is aided by three major salivary glands: The oral, parotid and submaxillary glands. By maintaining oral enzyme activity and pH, saliva modulates oral microbial flora. Oral glands produce viscous saliva with minimal enzymatic activity, whereas sub-maxillary and parotid glands create a watery discharge.

Saliva is useful for lubricating the oral cavity; it prevents tooth demineralization and makes swallowing easier. The salivary gland secretes about 0.5 L-2.0 L of saliva. However, 1.1 ml of saliva, which is always available, provides a comparatively low fluid volume available for drug release *via* delivery devices when compared to the GI tract. When GI fluid and saliva are compared, saliva is less viscous. The flow rate of saliva, which is determined by three factors: The time of day, the degree of stimulation and the type of stimulation. The route of absorption of any oral dose form through the mucosa is depicted in Figure 1 (Table 2) [4].

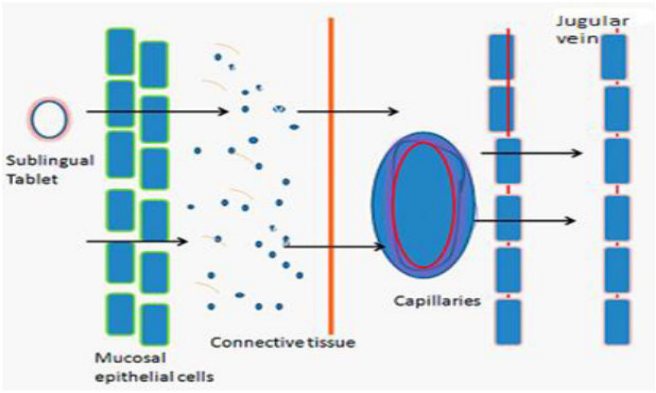

Figure 1: Mechanism of absorption through oral mucosa.

Table 2: Factors affecting the oral absorption.

Lipophilicity of drug	Lipophilicity is defined as a drug's affinity for a lipid environment. To be entirely absorbed *via* the oral route, a medicine must have somewhat higher lipid solubility than that required for GI absorption
Solubility in salivary secretion	In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e. biphasic solubility of the drug is necessary for absorption
pH of the saliva	As the mean of pH of saliva is 6.0, this pH promotes the absorption of medicines that are still unionised. Furthermore, medication concentration occurs through the oral mucosa if the range is larger than 2 for an acid and less than 10 for a base
Binding to oral mucosa	Drugs that bind to the mouth mucosa have a low systemic availability. In general, the higher a drug's lipophilicity, the stronger its binding to protein and the wider its distribution
Thickness of oral epithelium	Because the thickness of the oral epithelium is 100200 m, it is less than the thickness of the buccal epithelium. As a result of the thinner epithelium and drug immersion in a smaller volume of saliva, medication absorption is faster
Oil to water partition coefficient	Compounds with low oil-to-water partition coefficients are easily absorbed by the oral mucosa. The higher a substance's solubility, the higher its partition coefficient, and the higher the partition coefficient, the higher the membrane's permeability to that specific chemical

Advantages and disadvantages

Advantages:

- Oral spray provides faster onset and longer duration of action. It provides ease of administration to patients who refuse to take oral tablets/injectable.
- There is no requirement of tablet/capsule disintegration.
- Patients who experience dry mouth, the spray is a better substitute, since the dissolution of the spray is not dependent upon patient's saliva.
- Water does not require for swallowing the dosage form; elimination of first pass metabolism, good mouth feels property.
- Low dose provides high efficacy as hepatic first pass metabolism is avoided and also reduces the risk of side effects.
- Some drugs absorb from the mouth, pharynx and esophagus as the saliva passes down into the stomach, in such cases bioavailability of the drug increases.
- The large contact surface area of the oral cavity contributes to rapid and extensive drug absorption.
- It leads in improvement for patient compliance as the elimination of associated pain with injections reduces. The administration of drugs in unconscious or incapacitated patients can be possible and convenience of administration advances compared to injections or oral medications.

Disadvantages:

- Taste masking is a major problem associated with oral spray formulation.
- It is not applicable for drugs that require high blood levels or large doses.
- Oral delivery is not suited to sustained-delivery systems as it interferes with eating, drinking and talking.

Ideal properties of drug in oral drug delivery system:

- Drug should not bitter in taste.
- Dose should be lower than 20 mg, e.g. levocetrizine, ondacetron etc.
- Small to moderate molecular weight.
- Good stability in water and saliva.
- Undergoing first pass effect e.g. ketotifen fumarate.
- Drug should not ionize at the pH of oral cavities.
- Many drug properties that potentially affect the performance of drug like solubility, crystal morphology, particle size, bulk density etc.
- Some drugs undergo extensive first pass metabolism, which results in poor bioavailability in its oral dosage forms, that kind of drug is suitable for oral dosage form.
- Parenterally unstable preparations of the drug are suitable for oral dosage form.

Qualitative tests

Spray patterns: Deliver the spray through the container onto a whatmann filter paper (use color for better vision-brilliant blue) and observed the patterns formed and calculate the diameter and ovality ratio [5].

The ovality ratio is calculated using formula:

Ovality ratio=D_{max}/D_{min}

where,

D_{max} and D_{min} are the maximum and minimum diameters of the spray pattern respectively.

pH: A pH metre can be used to determine the pH. The pH metre is calibrated using two buffers per the manufacturer's instructions. After rinsing with water, the probe's tip is dipped into samples. Allow the metre to equilibrate. When the pH reaches equilibrium, it is recorde.

Leak test: A leak test was performed to ensure that the valve crimping was correct. To avoid faulty containers, crimping must be accessible. This was achieved by measuring the dimensions of the crimps and verifying that they met the criteria. By putting the full containers through a water bath, leak testing of valve closure was performed [6].

Quantitative tests

Density: The density of a liquid is an important quantity because it directly affects its flow ability. The pyknometer is weighed empty, then filled with 25 ml of the product and weighed again. The density of the product is calculated by dividing the difference between the filled and empty pyknometers by the volume filled.

Prime test: The priming test is performed by actuating the container until the formulation is released from the container. The number of actuations required for the container to release the formulation is counted [7].

Discharge rate: This is determined by taking a known weight product and discharging the contents for a certain period of time using standard equipment. After the time restriction has expired, reweighing the container yields the discharge rate, which can then be represented in grammes per second.

Net content: Empty containers are weighed before filling, then reweighed after filling and sealing and the difference is the net content [8].

Drug content: One ml of spray solution is taken and its absorbance is determined using UV spectrophotometer after adequate dilution. Concentration is determined from the standard plot and the drug content is calculated as a % of the theoretical value [9].

Drug content=Actual drug content/Theoretical drug content × 100

Drug content per spray: The content per spray is determined by firing two sprays in a beaker containing diffusion media. This solution is shaken for a few minutes and drug content is analyzed by analytical technique [10].

Spray angle: The method of impingement of spray on a bit of paper is employed for the work. Sudan red (10 mg) is dissolved in formulation to facilitate visualization. The sprays are actuated in horizontal direction onto a whole paper mounted at a specific distance from the nozzle. The radius of the circle, formed on the paper, is recorded in triplicate from different directions. Spray angle (θ) is calculated by equation [11].

Spray angle (θ)=tan-1 L/R

where,

L=Distance of paper from the nozzle; R=Average radius of the circle.

Spray profiling (Delivered dose uniformity): This USP-compliant test determines dose reproducibility. The median amount of active substance released by the actuator each spray is measured. The content unity is validated by running the test at three separate points, namely the beginning, middle and end [12].

Ex-vivo drug diffusion studies: The optimised formulation's *ex-vivo* drug diffusion investigation is carried out employing Franz diffusion. The experiment is carried out on oral goat mucosa in a buffer with a pH between 6 and 7. The aliquot is taken at the specified time interval and analysed in a UV spectrophotometer. The drug diffusion investigation is conducted over a set period of time [13].

Flux and apparent permeability determination: Flux and apparent permeability can be calculated using the following formulae [14].

Jss (Flux)=ΔQt/Δt × S

where,

ΔQt/S is the cumulative drug permeation per unit of mucosal surface area (μg/cm^2); t is time expressed in hour.

Papp (Apparent permeability)=Jss/Cd

where,

Jss is the flux and Cd is the concentrate of drug in donor compartment.

Stability studies: Stability testing is classified into two types: Electrochemical testing and long-term static testing. Electrochemical testing provides minimal information but is an effective screening tool. Long-term stability testing provides critical information such as weight loss, concentrate/propellant saturation changes (vapour pressure measurement), maintaining original spray characteristics, corrosion and concentrate stability (separation, coagulation, chemical change, gloss and odour change). Long-term static testing is typically done at a temperature of 30°C for three months to a year [15].

Conclusion

Oral drug administration through spray system offers various advantages, including rapid beginning of action, bypassing the liver, low dose yielding great efficacy and fast dissolution, making it suitable for both routine medicine and emergency situations. Advantages of novel drug delivery system are optimum dose at the right time and right location, efficient use of expensive drugs, excipients and reduction in production cost, beneficial to patients, better therapy, improved comfort and standard of living.

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Conflicts of Interest

Nil.

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