

Sublingual route for the systemic delivery of Ondansetron

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Abstract

Drug delivery via sublingual mucous membrane is considered to be a promising alternative to the oral route. This route is useful when rapid onset of action is desired as in the case of antiemetics such as ondansetron. In terms of permeability, the sublingual area of the oral cavity is more permeable than cheek and palatal areas of mouth. The drug absorbed via sublingual blood vessels bypasses the hepatic first-pass metabolic processes giving acceptable bioavailability with low doses and hence decreases the side effects. Sublingual drug delivery system is convenient for paediatric, geriatric, and psychiatric patients with dysphagia. This review highlights the different sublingual dosage forms, advantages, factors affecting sublingual absorption, pharmacology of ondansetron, methods of preparation and various in vitro and in vivo evaluation parameters of sublingual tablet of ondansetron.

Key words:

Sublingual route, ondansetron, dysphagia, improved bioavailability.

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INTRODUCTION-

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, peroral administration of drug has disadvantages such as hepatic first pass metabolism and enzymatic

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degradation within the GI tract, that limits oral administration of certain classes of drug like peptides and proteins. So, other absorptive mucosa are considered as potential sites for drug administration. Trans-mucosal routes of drug delivery (i.e. the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer several advantages over peroral administration for systemic delivery. These advantages include possible bypass of first pass effect, avoidance of pre-systemic elimination in GI tract and depending on drug suitable enzymatic flora for drug absorption. Within the oral cavity. Drug delivery can be classified in to three categories: (1) sublingual delivery, systemic delivery of drug beneath the tongue, (2) buccal delivery, drug administration through the linings of cheeks i.e. buccal mucosa, and (3) local delivery, which is drug delivery into oral cavity for local action. sublingual is a latin word which means under the tongue and refers to the pharmacological [route of administration](#) by which [drugs](#) diffuse into the blood through tissues under the tongue. Many pharmaceuticals are designed for sublingual administration, including cardiovascular drugs, steroids, barbiturates, enzymes, and increasingly, vitamins and minerals.^[1-3]

Mechanism of absorption-

Systemic drug delivery via sublingual route had emerged from the desire to provide immediate onset of pharmacological effect. Dysphagia (difficulty in swallowing) is a common problem of some age groups, especially elderly, children, and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid intake/ diets have difficulties in swallowing these dosage forms^[4, 5]. Upon sublingual administration drug reaches directly in to the blood stream through the ventral surface of the tongue and floor of the mouth. The drug solutes are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and transported

through the facial veins, internal jugular vein, and brachiocephalic vein and then drained in to systemic circulation. The main mechanism for the absorption of the drug in to oral mucosa is via passive diffusion into the lipoidal membrane^[6]. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route and is only surpassed by hypodermic injection. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. Sublingual absorption is mostly rapid in action, but also short acting in duration. for example, Nitroglycerine is an effective antianginal drug but is extensively metabolized when taken orally (>90%). It is rapidly absorbed through the sublingual mucosa, and its peak plasma level is reached within 1-2 min. Because of its short biological half life (3-5 min.), however the blood concentration of nitroglycerine declines rapidly to a level below the therapeutic concentration within 10-15 min. In terms of permeability, the sublingual area of the oral cavity is more permeable than the buccal (cheek) area, which in turn is more permeable than the palatal (roof of the mouth) area. The differences in permeability are generally based on the relative thickness, the blood supply, and degree of keratinization of these membranes^[7-8].

ADVANTAGES-

- Mesenteric circulation is by-passed so there is no loss of drug by first pass effect.
- Higher bioavailability and onset of action compare to oral route.
- Rapid absorption due to high vascularization beneath the tongue.
- Reduce the side effect due to low dose and high efficacy.
- Provide fast dissolution or disintegration in oral cavity without water or chewing action.
- pH in the mouth is relatively neutral so drug will be more stable.
- Improved patient compliance.

- Relatively large contact surface area provides rapid and extensive absorption.

DISADVANTAGES-

- sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.
- Holding the dose in mouth is inconvenient, if any is swallowed that portion must be treated as an oral dose and subjected to first pass metabolism.
- Only small doses can be accommodated easily.
- Not suitable for sustain release formulations.
- It can not be used when patient is uncooperative or unconscious.
- The patient should not smoke while taking sublingual medication, because smoking causes vasoconstriction of the blood vessels. This will decrease the absorption of the medication.

SUITABILITY OF DRUG FOR PREPARATION OF SUBLINGUAL TABLET-

- For the drug delivering through sublingual route should have following property.
 - No bitter taste
 - Dose lowers than 20mg, e.g. nifedipine
 - Small to moderate molecular weight
 - Good stability in water and saliva
 - Partially non ionized at the oral cavities pH
 - Undergoing first pass effect e.g. ketotifen fumarate
- Many drug properties could potentially affect the performance of sublingual tablets like solubility, crystal morphology, particle size, hygroscopicity, compressibility and bulk density of drug.

- Some drugs undergoes extensive first pass metabolism which results in poor bioavailability of its oral dosage forms, that kind of drugs are suitable for sublingual dosage form.
- Drugs that are unstable in parenteral preparation are suitable for sublingual dosage form.
- Many pharmaceuticals are designed for sublingual administration, including cardiovascular drugs, steroids, barbiturates, enzymes, antiemetics, vitamins, minerals and vaccines.

FACTORS AFFECTING ABSORPTION^[9] -

- Lipophilicity of drug: For a drug to be absorbed completely through sublingual route, the drug must have slightly higher lipid solubility than that required for GI absorption is necessary for passive permeation.
- Solubility in salivary secretion: In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e. biphasic solubility of drug is necessary for absorption.
- pH and pKa of the saliva: As the mean pH of the saliva is 6.0, this pH favors the absorption of drugs which remain unionized. Also, the absorption of the drugs through the oral mucosa occurs if the pKa is greater than 2 for an acid and less than 10 for a base.
- Binding to oral mucosa: Systemic availability of drugs that bind to oral mucosa is poor.
- Thickness of oral epithelium: As the thickness of sublingual epithelium is 100-200 μm which is less as compared to buccal thickness. So the absorption of drugs is faster due to thinner epithelium and also the immersion of drug in smaller volume of saliva.

- Oil to water partition coefficient: Compounds with favorable oil-to-water partition coefficients are readily absorbed through the oral mucosa. An oil-water partition coefficient range of 40-2000 is considered optimal for the drugs to be absorbed sublingually.

Different formulations for sublingual drug delivery system-

- Fast-disintegrating sublingual tablets
- Bioadhesive sublingual tablet
- Thin film drug delivery
- Lipid matrix sublingual tablet
- Sublingual immunotherapy
- Sublingual vitamin tablet

PHARMACOLOGY OF ONDANSETRON^[10] -

Ondansetron is a [serotonin 5-HT₃ receptor antagonist](#) used mainly as an [antiemetic](#) (to treat [nausea](#) and [vomiting](#)), often following [chemotherapy](#). Its effects are thought to be on both peripheral and central nerves. Ondansetron reduces the activity of the [vagus nerve](#), which deactivates the vomiting center in the [medulla oblongata](#), and also blocks serotonin receptors in the [chemoreceptor trigger zone](#). It has little effect on vomiting caused by motion sickness, and does not have any effect on [dopamine](#) receptors or [muscarinic receptors](#).

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations are attained approximately 1.5 hours after dosing. For doses above 8mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses.

Bioavailability is slightly enhanced by the presence of food but unaffected by antacids. The disposition of ondansetron following oral, intramuscular or

intravenous dosing in adults is similar with a terminal elimination half-life of about 3 hours and steady state volume of distribution of about 140L. Ondansetron is not highly protein bound (70-76%). Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5% of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (5 h) of ondansetron.

TECHNIQUES^[11-16] –

Direct compression-

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. Directly compressed tablet's disintegration and solubilization are strongly affected by tablet size and hardness. This technique can now be applied to fast dissolving tablets because of the availability of improved tablet excipients, especially superdisintegrants like cross carmellose sodium, microcrystalline cellulose, croscopolvidone, sodium starch gluconate and partially substituted hydroxypropyl cellulose, effervescent agents (citric acid, sodium bicarbonate) and sugar-based excipients (dextrose, fructose, isomalt, maltitol, maltose, mannitol, sorbitol, starch hydrolyse, polydextrose, and xylitol)

Tablet moulding-

In this technology, water soluble ingredients are used so that tablet disintegrate and dissolve rapidly. The powder blend is moistened with a hydro alcoholic solvent and is molded in to tablet using compression pressure lower than used in conventional tablets compression. The solvent is then removed by air drying. Two problems commonly encountered are mechanical strength and poor taste masking characteristics. Using binding agents such as sucrose, acacia or poly vinyl pyrrolidone can increase the mechanical strength of the tablet.

Spray drying-

Spray drying produces highly porous and fine powder as the processing solvent is evaporated during process. Spray dryers are widely used in pharmaceuticals and biochemical process. Spray drying can be used to prepare rapidly disintegrating tablets by using support matrix such as hydrolysed an non hydrolysed gelatin and other components like mannitol as bulking agent, sodium starch glycolate, cross carmelose sodium as disintegrants, acidic material like citric acid and alkali like sodium bicarbonate to enhance disintegration and dissolution.

Taste masking-

Taste masking is an essential requirement for fast dissolving tablets for commercial success. Taste masking of the active ingredients can be achieved by various techniques. Drugs with unacceptable bitter taste can be microencapsulated into pH sensitive acrylic polymers. Cefuroxime axetil is microencapsulated in various types of acrylic polymers (e.g., Eudragit E, Eudragit L-55 and Eudragit RL) by solvent evaporation and solvent extraction techniques. These polymer microspheres showed efficient taste masking and complete dissolution in a short period. Fine granules of drug and disintegrant (e.g. low substituted hydroxypropyl cellulose) when coated with a water insoluble polymer (e.g. ethylcellulose) masked the bitter taste

of ondansetron. The addition of low substituted hydroxypropyl cellulose as disintegrant to the drug in cores, resulted in increased dissolution rate and bioavailability of sparfloxacin compared to its conventional tablets.

Freeze drying-

Lyophilization can be used to prepare tablets that have very porous open matrix network into which saliva rapidly disperses when placed in mouth. The drug is entrapped in a water soluble matrix which is freeze dried to produce a unit which rapidly disperses when placed in mouth. Apart from the matrix and active constituents, the final formulation may contain other excipients, which improve the process characteristics or enhance the quality of the final product. These include suspending agents, wetting agents, preservatives, antioxidants, colours and flavours. The preferred drug characteristics for freeze drying formulations are water insoluble, low dose, chemically stable, small particle size and tasteless. Lyophilization is relatively expensive and time consuming manufacturing process. Other drawbacks include fragility, which make the use of conventional packing difficult and poor stability during storage and stressful condition.

Mass Extrusion-

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking bitter taste.

Sublimation-

The basic principle involved in preparing fast dissolving tablets by sublimation technique is addition of a volatile salt to the tableting component, mixing the components to obtain a substantially homogenous mixture and volatilizing salt. The removal of volatilizing salt creates pores in the tablet,

which help in achieving rapid disintegration when the tablet comes in contact with saliva. The tablets were then subjected to vacuum at 80° C for 30 minutes to eliminate volatile components and thus create pores in the tablet. Volatile salts such as camphor, ammonium bicarbonate, naphthalene, urea, etc., were also used as sublimable components to prepare porous.

EVALUATION^[17-34] -

Tablets from all the formulation can be subjected to following quality control test.

General Appearance-

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Include in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and Shape-

The size and shape of the tablet can be dimensionally described, monitored and controlled.

Tablet thickness-

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

Uniformity of weight-

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The limit for weight variation is given in Table 1.

Table 1: IP limit for weight variation

Avg Weight of tablet	% variation allowed
80mg or less	10
60mg but < 250mg	7.5
250mg or more	5

Tablet hardness-

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester.

Friability-

It is measured of mechanical strength of tablets. Roche friabilator can be used to determine the friability by following procedure. A preweighed tablet was placed in the friabilator. Friabilator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 minutes. At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{Friability} = \text{loss in weight} / \text{Initial weight} \times 100$$

Wetting time-

A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined.

Surface pH-

The surface pH of the tablets was determined in order to investigate the possibility of any side effects due to change in pH *in vivo*, since an acidic or alkaline pH may cause irritation to the buccal mucosa. A combined glass electrode was used for the purpose. The tablets were allowed to swell by keeping them in contact with 1.0 ml of simulated saliva for 2 hours and pH was noted by bringing the electrode in contact with the surface of the formulations and allowing it to equilibrate for 1.0 min.

In-vitro dispersion time-

In-vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

In-vitro Disintegration test-

The test was carried out on 6 tablets using the apparatus specified in I.P. 1996 distilled water at $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$ was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

Stability testing of drug (temperature dependent stability studies)-

The fast dissolving tablets are packed insuitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

- (i) $40 \pm 1^{\circ}\text{C}$
- (ii) $50 \pm 1^{\circ}\text{C}$
- (iii) $37 \pm 1^{\circ}\text{C}$ and RH $75\% \pm 5\%$

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations, Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the

kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C .

CONCLUSION-

Recently ondansetron have been formulated for sublingual drug delivery with an objective of rapid drug release and restricting the region of drug release to mouth. Compared to commonly used tablets, capsules and other oral dosage forms, sublingual absorption is generally much faster and more efficient. Sublingual dosages are convenient for young children, the elderly and patients with swallowing difficulties, and in situations where potable liquids are not available. Peak blood levels administered sublingually are achieved within 10-15 minutes, which is generally much faster than when ingested orally. Sublingual absorption is efficient. The percent of each dose absorbed is generally higher than that achieved by means of oral ingestion. Various types of sublingual dosage forms of ondansetron are available in market like tablets, films and sprays.

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