International Journal of Current Trends in Pharmaceutical Research
CODEN (USA): IJCTGM | ISSN: 2321-3760
Journal Home Page: www.pharmaresearchlibrary.com/ijctpr

REVIEW ARTICLE

A brief review on sublingual drug delivery system

Ajay Raj Yadav*, Rahul Kumar Singh[1]

Department of Pharmaceutics, Rajiv Academy for Pharmacy, N.H. #2, Mathura Delhi Road, P.O. CHHATIKARA, Mathura, Uttar Pradesh 281001

ABSTRACT

In Sublingual drug delivery system drug are placed under the tongue. Drugs are fastly absorbed by the oral mucosa which is directly reached in the systemic circulation. The main advantage of the sublingual system is easily administrate by the patient and bypasses hepatic first pass metabolic process which gives better bioavailability, rapid onset of action, patient compliance, self-medicated. The absorption of drug through sublingual route is 3-10 times greater than that given oral route. In this review article highlight the sublingual dosage forms, factors affecting the sublingual absorption, advantages, evaluation method.

Keyword: Sublingual, advantage, dosage form, evaluation.

ARTICLE INFO

Corresponding Author
Ajay Raj Yadav
Department of pharmaceutics,
Rajiv academy for pharmacy, N.H. #2,
Mathura, Uttar Pradesh 281001
MS-ID: IJCTPR4003

JOURNAL QR-CODE

Article History: Received 05 Oct 2019, **Accepted** 21 Nov 2019, **Available Online** 15 Jan 2020

Citation: *Ajay Raj Yadav*, *et al.* A brief review on sublingual drug delivery system. *Int. J. Curnt. Tren. Pharm, Res.*, 2020, 8(1): 07-11.

CONTENTS

1. Introduction 07
2. Evaluation Methods. 09
3. Conclusion. 10
5. References. 10

1. Introduction

Systemic drug delivery through the sublingual route provide immediate onset of pharmacological effect. Dysphasia (difficulty in swallowing) is a measure problem of elderly, children, and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid intake/ diets have difficulties in swallowing these dosage forms. [(1)] Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly in to the blood stream .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 bracio cephalic vein and then drained in to systemic circulation. Sublingual delivery of a drug and its further absorption depends on the permeability of the sublingual membrane, the physicochemical properties of a drug, and the design of the dosage form. This review article focuses on the physicochemical properties and the

formulation design because a perceptive of these elements enables the assortment of suitable drug molecules for 3 sublingual delivery and optimization of the final formulation .(2) Oral mucosal drug delivery is an alternative method that offers several advantages because the oral mucosa is highly vascularised that drugs are absorbed through the oral mucosa directly enter the systemic circulation, by passing the GIT and first-pass metabolism in the liver.(3) Sublingual administration of the drug reaches directly in to the blood stream through the floor of the mouth and ventral surface of the tongue. Drug get rapidly absorbed into the reticulated vein which lies underneath the buccal Mucosa and transported through the facial veins, braciocephalic vein and internal jugular vein and then drained in to systemic circulation.(4) The small volume of saliva is sufficient to result in disintegration of the tablet in the oral cavity. Sublingual absorption is mostly rapid in action, but also short acting in duration. (5)

Advantage

1. Rapid onset of action is achieved as compared to the oral route.
2. Liver is bypassed and also drug is protected from metabolism due to digestive enzymes of the middle gastro intestinal tract.
3. Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients; convenience of administration as compared to injections or oral medications.
4. Low dosage gives high efficacy as hepatic first pass metabolismis avoided and also reduces the risk of side effects.
5. Due to rapidity in action these sublingual dosage forms are widely used in emergency conditions e.g. asthma

Disadvantage

1. Since sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.
2. Although this site is not well suited to sustained-delivery systems.
3. Sublingual medication cannot be used when a patient is uncooperative or unconscious.
4. 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.(6)

Sublingual gland:

Sublingual glands are also known as the salivary glands which are present in the floor of mouth underneath the tongue. These glands produce mucin and help to promote the production of saliva. Because of the secretions of the glands, the interior area of the mouth is kept lubricated, which is necessary for chewing and swallowing food. The lubrication and binding functions of the sublingual glands cannot be underestimated. A secretion from the glands mix with food as it is chewed, making the material slippery and easily swallowed. Because of the saliva content of the masticated food, it can move without difficulty into the throat and on to the digestive tract. Low levels of saliva production can make the process of swallowing much more difficult and will increase the potential for food to lodge in the throat. Along with providing lubrication, these glands also aid in the promotion of good oral hygiene. Absorption means transfer of drug from its site of administration to the systemic circulation, so it is obvious that absorption is directly proportional to the membrane layer thickness. Sublingual > Buccal > Gingival > Palatal having mucosa thickness of 100-200, 200, 250, 500-600 micrometer respectively. Because of the high permeability and the rich blood supply, the sublingual route is capable of producing a rapid onset of action which makes it an appropriate route for drugs with short delivery period and in frequent dosing regimen. The drug is released in to saliva and its subsequent spreading may cause the drug to be absorbed across the oral cavity. (7).

Mechanics of sublingual absorption:

The absorption potential of oral mucosa is influenced by the lipid solubility and therefore the permeability of the solution (osmosis); the ionization (pH); and the molecular weight of the substances. For example, absorption of some drugs via oral mucosa is shown to increase when carrier pH is lowering (more acidic) and decrease with a lowering of pH (more alkaline) (8, 9).

The cells of the oral epithelium and epidermis are also capable of absorbing by endocytosis (the uptake of particles by a cell as if by hollowly wrapping itself around it. These engulfed particles are usually too large to diffuse through its wall). It is unlikely that this mechanism is used across the entire stratified epithelium. It is also unlikely that active transport processes operate within the oral mucosa. However, it is believed that acidic stimulation of the salivary glands, with the accompanying vasodilatation, facilitates absorption and uptake into the circulatory system. The mouth is lined with a mucous membrane which is covered with squamous epithelium and contains mucous glands. The sublingual mucosal tissue is similar to that of buccal mucosa (10).

The salivary glands consist of lobules of cells which secrete saliva through the salivary ducts into the mouth. The three pairs of salivary glands are the parotid, the submandibular and the sublingual which lies on the floor of the mouth. The more acid the taste, the greater the stimulation of salivary output; serving to avoid potential harm to acid-sensitive tooth enamel by bathing the mouth in copious neutralizing fluid.

The sublingual artery travels forward to the sublingual gland, it supplies the gland and branches to the neighbouring muscles and to the mucous membranes of the mouth, tongue and gums. Two symmetrical branches travel behind the jawbone under the tongue to meet and join at its tip. Another branch meets and anatomises with the sub mental branches of the facial artery. The sublingual artery stems from the lingual artery the body's main blood supply to the tongue and the floor of the mouth which arises from the external carotid artery. The proximity with the internal carotid artery allows fast access to its route supplying the greater part of the cerebral hemi sphere (11, 12).

Drugs for sublingual administration:

Sublingual drug administration is applied in the field of cardiovascular drugs, steroids, some barbiturates and enzymes. It has been a developing field in the administration of many vitamins and minerals which are found to be readily and thoroughly absorbed by this method. Sublingually absorbed nutrition, which avoids exposure to the gastric system and liver, means direct nutritional benefits, particularly important for sufferers of gastro-intestinal difficulties such as ulcers, hyperactive gut, coeliac disease, those with compromised digestion, the elderly and invalids – the nutritional benefit is independent of gastro-intestinal influences [13, 14]. Examples of drugs administered by this route include antianginal like nitrites and nitrates, anti-hypertensive like nifedipine, analgesics like morphine and bronchodilators like fenoterol. Certain steroids like estradiol and peptides like oxytocin can also be administered e.g. fentanyl citrate, apomorphine, prochlorperazine dimaleate {PRO}, and hydrazine HCl {HYD}.

Factors affecting the sublingual absorption [15]

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 favourable 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.

Method of preparation of sublingual formulations:

Sublingual Tablets:

Direct compression is one of the techniques which require the incorporation of a super disintegrant into the formulation, or the use of highly water- soluble excipients to achieve fast tablet disintegration. It is the ideal method for moisture and heat-labile medications. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. Directly compressible tablet's disintegration and solubilisation depends on single or combined action of disintegrates, water soluble excipients and effervescent agent. Disintegration efficacy is strongly affected by tablet size and hardness [16]

Films:

Solvent casting is a process which comprises of casting a dope from a casting die onto a casting support, drying the cast dope on the casting support form film, stripping off the film from the casting support, and further drying the film whileconveying the film with carrying it at both side edges of the film by a pin tenter, wherein residual volatile component content of both side edges of the film being carried by the pin tenter is from 30 to 320 mass % of solid matter at the beginning of being cared by the pin tenter. Solvent Evaporation technique can also be used instead of solvent casting for the preparation of sublingual films. Sublingual sprays are also in trend which improves the time to reach maximum plasma concentration as compared to other types of sublingual dosage forms. E.g. in case of oxycodone, maximum plasma concentrations is reached within 20 min when compare with immediate release oral tablets (1.3 h), intramuscular (1 h), and intranasal oxycodone (0.42 h) in healthy volunteers [17].

2. Evaluation methods

Weight variation:

It was performed as per the method given in the Indian pharmacopoeia. Tablets were randomly checked to ensure the proper weight tablets were being made. Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated. [18]

Friability:

The 20 tablets were weighed and placed in the roche friabilator test apparatus, the tablets were exposed to rolling and repeated shocks, resulting from free falls within the apparatus. After 100 revolutions the tablets were de-dusted and weighted again. The friability was determined as the percentage loss in weight. [19]

$$\% \text{ Friability} = \frac{\text{Initial weight-Final weight}}{\text{Initial wt. of tablet}} \times 100$$

Hardness:

Hardness was measured using the Monsanto or Pfizer hardness tester. Measure the pressure required to break diametrically placed tablet, by a coiled spring. The result of weight variation was shown in table [20]

***In-vitro* disintegration studies:**

Initially the disintegration time for fast dissolving tablets was measured using the conventional test for tablets as described in the Pharmacopoeia. Tablets were placed in the disintegration tubes and time required for complete disintegration, that is without leaving any residues on the screen was recorded as disintegration time. A modified method was also used to check the disintegration time. In about 3 tablets were tested from each formulation. In disintegration time study tablet was put into the 100 ml pH 6.8 phosphate buffer containing beaker at the 37±2°C. Tablet was placed in the cylinder and time required for the complete dispersion of tablet in the cylinder was recorded as the disintegration time. [18]

Wetting time:

The tablets wetting time was measured by a procedure modified from that reported by Bi et al. The tablet was placed at the centre of two layers of absorbent paper attend

into a dish. After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch. [21]

Water absorption ratio:

A piece of tissue paper folded twice was placed in a small petric dish containing 6ml of water. A tablet was put on the tissue paper and allowed to wet completely. The wetted tablet was then weighed. Water absorption ratio R was determined using following equation. [22]

$$R = \frac{Wa-Wb}{Wb} \times 100$$

Where, Wa = Weight of the tablet after wetting.
Wb= Weight of the tablet before wetting.

Uniformity of Content:

Five tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 10 mg of drug was weighed and dissolved in 100 ml of pH 6.8 phosphate buffer, this was the stock solution from which 1 ml sample was withdrawn and diluted to 10 ml with pH 6.8 phosphate buffer, the absorbance was measured at wavelength using double beam UV-Visible spectrophotometer. [23]

Content uniformity was calculated using formula:

$$\% \text{ Purity} = 10\ C\ (Au / As)$$

Where, C – concentration
Au and as – absorbance of unknown and standard respectively

***In-vitro* drug release study:**

Literature reveals that dissolution of sublingual tablets should be seen in pH 7.4. Dissolution studies were carried out for optimized formulation employing USP dissolution testing apparatus (TDT-08L, Electro lab, mumbai) type II paddle method. The dissolution medium (900 ml) at 100 rpm and 37 ± 0.5ºC. A 5 ml of sample was periodically withdrawn at 0, 2, 5, 10, 15, 20; 30 min. and volume replaced with equivalent amounts of same dissolution medium to maintain sink condition. The samples were analyzed spectrophotometrically a by using pH 6.8 Phosphate buffer as a blank and drug content in dissolution sample were determined by using calibration curve. The UV visible spectrophotometer (UV 3000+ Labindia, Mumbai) was used to measured absorbance [24].

4. Conclusion

Sublingual dosage form have the benefit for patient by the improve the drug compliances and increase the bioavailability. Sublingual route by pass the hepatic first pass metabolism which degraded the drug and reduces the bioavailability of drug. In the review article studies the various dosage forms which provided through this routes. Sublingual dosage form provided the fastly action of drug in comparison of other conventional oral dosage form like capsule, syrups, solution and tablets. Different types of sublingual dosage form available in market like tablets spray film and etc.

5. References

[1] Journal: Ishikawa T, Koizumi N, Mukai B. Pharmacokinetics of acetaminophen from rapidly disintegrating compressed tablet prepared using microcrystalline cellulose (PH-M-06) and spherical sugar granules. Chem Pharm Bull (Tokyo) 2001; 49: 230-32.

[2] Journal: Squier CA, Wertz PW. Structure and function of the oral mucosa and implications for drug delivery. Drugs Phar Sci. 1996; 74:1-26.

[3] Journal: Patel KN, Pancholi SS. Pancholi. An overview on: Sublingual route for systemic drug delivery. International Journal of Research in Pharmaceutical and Biomedical Sciences. 2012; 3(2):913-23.

[4] Journal: Narang N, Sharma J. Sublingual mucosa as a route for systemic drug delivery. Int J Pharm Sci. 2011; 3(2).

[5] Journal: Patil VA, Darekar AB, Saudagar RB. Review article on sublingual route drug delivery system. World Journal of Pharmaceutical Research. 2014; 4(6):503-13.

[6] Journal: Neha Narang, Jyoti Sharma sublingual mucosa as a route for systemic drug delivery. International journal of pharmacy and pharmaceutical sciences. Vol 3, suppl 2, 2011; 18-22.

[7] Journal: Shojaie AH. Buccal mucosa as a route for systemic drug delivery: A review. J Pharm Sci 1998; 1(1):15-30.

[8] Journal: Richman MD, Fox D, Shangraw RF. Preparation and stability of glyceryltrinitrate sublingual tablets prepared by direct compression. J Pharm Sci 1965; 54(3):447-451.

[9] Journal: McElnay JC, Al-Furaih TA, Hughes CM, Scott MG, Elborn JS, Nicholl DP. The effect of pH on the buccal and sublingual absorption of captopril Eur J Clin Pharmacol 1995; 48(5): 373-379.

[10] Journal: Boer D et al. Drug absorption by sublingual and rectal routes. British J Anaesthesia 1984; 56: 69-82.

[11] Journal: Mary Elizabeth RN, Martelli BS. Sublingual and buccal medication administration. Encyclopedia of Nursing and Allied Health, 20050229.

[12] Journal: Lea L. Sublingual Administration. Colon Health 1996; 13.

[13] Jounral: Boer D et al. Drug absorption by sublingual and rectal routes. British JAnaesthesia 1984; 56: 69-82.

[14] Journal: Al-Ghananeem AM, Malkawi AH, Crooks PA. Effect of pH on Sublingual absorption of Oxycodone Hydrochloride. AAPS PharmSciTech 2006; 7(1): Article 23.

[15] Journal: Katz M, Barr M. A study of sublingual absorption I. Several factors influencing the rate of adsorption. J Am Pharm Assoc Am Pharm Assoc (Baltim) 1955; 44(7): 419-423.

[16] Journal: Peh KK, Wong CF. Polymeric films as vehicles for buccal delivery; swelling, mechanical, and bioadhesive properties. J Pharm Sci. 1999; 2: 53-61.
[17] Journal: Bi Y, Sunada H, Yonezawa Y, Danjo K, Otsuka A, Iida K. Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. Chem Pharm Bull. 1996; 44: 2121-2127.
[18] Book: United States of Pharmacopeia-National Formulary. USP 32 – N F 27. The United States Pharmacopoeia Convention, Rockville, MD., 53-54. (2004).
[19] Book: Indian Pharmacopoeia, Government of India, Ministry of Health and Family Welfare, Published by the Controller of Publication, New Delhi. II, pp. 442. (2007).
[20] Book: Ansel, H.C., Introduction to Pharmaceutical Dosage Form, fourth ed., K.M Varghese Company, Bombay, 146-158. (2005).
[21] Journal: Edmund J: Preparation, characterization and scale of ketoconazole with enhanced dissolution and bioavailability. Drug Development Industrial Pharmacy. 2007; 3:755-765.
[22] Journal: Chaudhari, P.D., Chaudhari, S.P., Lanke, S.D., Patel, N., Indian. J. Pharm. Edu. 41, 4, 319-27. (2007)
[23] Book: Indian Pharmacopoeia. Government of India, Ministry of Health and Family Welfare, Published by the Controller of Publication, New Delhi. II, pp. 663-665. (2007).
[24] Journal: Bharadwaj V., Shukla V., Goyal N., Salim M.D., Sharma P.K., Int J Pharmacy Pharm Sci, Vol 2, Issue 3, 89-92.(2002).