# A COMPREHENSIVE REVIEW ON SUBLINGUAL DRUG DELIVERY SYSTEM

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**Abstract**

Sublingual drug delivery is a unique method of delivering drugs to the body. In this method, medications are administered by placing them under the tongue, where they dissolve and enter the bloodstream directly, avoiding first pass effect. This method of drug delivery has several advantages over other routes of administration, such as oral or injectable routes. One of the key benefits is its higher bioavailability, as the drug is absorbed directly into the bloodstream. This results in a rapid onset of action. Sublingual drug delivery also has a reduced risk of side effects, as the medication bypasses the digestive system, which can often cause unwanted reactions. Additionally, this method of delivery can also improve patient compliance, as it eliminates the need for injections or swallowing large pills.

In this review article, various topics are included for instance, mechanism of action, advantages and disadvantages of route, ideal properties, factor affecting sublingual route, preparation of sublingual tablets, evaluation of formulation, future prospective and challenges. Despite its advantages, sublingual drug delivery also has limitations. The amount of medication that can be delivered through this route is limited, and some drugs are not suitable for sublingual delivery due to their properties. This review article aims to provide a comprehensive overview of sublingual drug delivery, including its mechanism of action, advantages and limitations, evaluation parameters, challenges and future prospective and recent development. By highlighting the potential of sublingual drug delivery, this review hopes to encourage further research and development in this area of drug delivery.

**Keywords:** Sublingual, First Pass Effect, Mechanism Of Action, Recent Development.

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## 1. Introduction

Local drug delivery in the oral cavity can be targeted at various sites, including the buccal, sublingual, periodontal, tongue, and gum regions, as well as adjacent areas like the pharynx, larynx, adenoids, and tonsils. There are three categories of drug delivery via the membranes of the oral cavity: sublingual, buccal, and local delivery. Sublingual delivery involves placing the drug under the tongue, where it is rapidly absorbed into the blood stream through the mucosal membranes lining the floor of the mouth. This route of administration typically produces a faster onset of action than orally ingested tablets, and the portion absorbed through the sublingual blood vessels bypasses the liver's first-pass metabolic processes. The main mechanism for drug absorption into the oral mucosa is passive diffusion into the lipoidal membrane. This method is especially useful for those who have difficulty swallowing, such as the elderly, children, and psychiatric patients. The sublingual area is more permeable than the buccal and palatal areas, making it a preferred site for drug absorption. [1,2] However, the sublingual mucosal membrane is highly permeable to certain types of drugs, such as those with a high lipophilicity and low molecular weight. The permeability is due to the presence of a thin and highly vascularized mucosal layer that contains a large number of capillaries, which allows for rapid absorption of the drug into the bloodstream. The sublingual route of drug delivery avoids the first-pass metabolism in the liver, leading to higher bioavailability of the drug. Despite the high permeability of the sublingual membrane, some compounds may not be suitable for sublingual administration due to their physicochemical properties or the potential for irritation or damage to the oral mucosa. Therefore, careful consideration and formulation optimization are necessary when developing sublingual drug delivery systems. [3,4] Salivary gland hypofunction can cause a decrease in oral pH, leading to a higher ionized fraction of fentanyl and lower lipophilicity. This condition is also associated with various oral mucosal disorders that can increase or decrease the permeability of the oral mucosa. Additionally, saliva plays a crucial role in dissolving oral transmucosal formulations.[5]

**Mechanism of Action of Sublingual absorption**

The mucosal lining in the sublingual region consists of three layers, with the outermost layer being the epithelial membrane that acts as a protective barrier. Beneath the epithelium lies the less dense and hydrated layer of connective tissue called the lamina propria, followed by the submucosa which is richly supplied with blood vessels. [6]

The sublingual mucosa and intestinal epithelium membrane have similar drug permeation mechanisms, with two main pathways involved: transcellular and intercellular. Lipophilic drugs with higher LogP values mostly use the transcellular pathway, which depends on their partition coefficient. Hydrophilic drugs typically pass through the intercellular pathway, which involves the diffusion of compounds through intercellular lipids. Carrier systems are less common and not well understood, and there may be additional specialized transport mechanisms.[7]

**Factor affecting Sublingual absorption [8-10]**

The successful absorption of a drug through the buccal or sublingual mucosa depends on several factors.

### 1.1 Solubility

The drug should possess high lipid solubility and be soluble in the aqueous buccal fluids for biphasic solubility, which is necessary for absorption. Drugs that bind to the oral mucosa have poor systemic availability.

### 1.2 Thickness of epithelium

The thickness of the oral epithelium affects drug absorption. The sublingual epithelium is thinner, with a thickness of 100-200 μm, compared to the buccal epithelium. As a result, drug absorption is faster due to the thinner epithelium and the immersion of the drug in a smaller volume of saliva.

### 1.3 Degree of Ionization, pH, and Lipid Solubility

The lipid solubilities depends upon the permeabilities of unionized compound. Lipidsolubilities determined by their partition coefficient and demonstated by dependance of waterpermeability on the lipid contnets of keratinized and non- keratinized epithelia. The absorption of drugs through a membrane depends on their lipophilicity, which is influenced by theirdegree of ionization and partition coefficient. Higher unionized fractions of a drug increase its lipid solubility, while the degree of ionization depends on pH and pKa values. Beckett andTriggs found that absorption increased as the concentration of the unionized drug increasedand absorption curves varied based on pKa values and lipid solubility.

**1.4 Flow of saliva:**
Saliva plays vital role in disintegration and dissolution of the formulation. If saliva flow is less, mouth becomes dry which can lead to alter the drug absorption through mucosa. In contrast, if flow is high, formulation being swallowed before absorption.

**Different formulations for sublingual drug delivery system [11]**
- Fast-disintegrating sublingual tablets
- Bioadhesive sublingual tablet
- Thin film drug delivery
- Lipid matrix sublingual tablet
- Sublingual immunotherapy
- Sublingual vitamin tablet

## 2. Manufacturing techniques used in sublingual tablet Formulation [12]

**2.1 Direct Compression**
Direct compression is indeed one of the easiest and most widely used methods for manufacturing tablets. The process involves mixing the active ingredient with various excipients, such as fillers, binders, and lubricants, to form a homogeneous blend that can be compressed into a tablet.

**2.2 Tablet Molding**
Wet granulation is commonly used for tablets that need to disintegrate and dissolve rapidly, as the moistening step can help to improve the tablet's solubility. However, it can lead to problems with mechanical strength and taste masking.

**2.3 Spray drying**
Spray drying is a technique that produces fine, porous powder by evaporating the processing solvent. It is widely used in pharmaceuticals and biochemical processes. Spray drying can be used to prepare rapidly disintegrating tablets by adding support matrix such as hydrolysed or non-hydrolysed gelatin, and components like mannitol as a bulking agent, disintegrants like sodium starch glycolate and cross carmelose sodium, and acidic materials like citric acid and alkali like sodium bicarbonate to improve disintegration and dissolution.

**2.4 Taste Masking**
Taste masking is crucial for the commercial success of fast dissolving tablets, and various techniques can be used to achieve it. One such method is microencapsulation of drugs with pH sensitive acrylic polymers like Eudragit E, Eudragit L-55, and Eudragit RL using solvent evaporation or solvent extraction techniques. Another approach is to coat fine granules of the drug and disintegrant with a water-insoluble polymer like ethylcellulose to mask the bitter taste.

**2.5 Freeze Drying**
Lyophilization is a technique that can be used to prepare tablets with a porous open matrix network that disperses rapidly in the mouth. The drug is entrapped in a water-soluble matrix that is freeze-dried to produce the tablet. Other excipients can be added to improve the process or enhance the product's quality, including suspending agents, wetting agents, preservatives, antioxidants, colors, and flavors.

**Mass Extrusion**
This technology involves using a solvent mixture of water-soluble polyethylene glycol and methanol to soften the active blend. The softened mass is then expelled through an extruder or syringe to form a cylinder, which is cut into even segments using a heated blade to produce tablets. The dried cylinder can also be used to coat granules of bitter-tasting drugs to mask their taste.

**Sublimation**

The sublimation technique for preparing fast-dissolving tablets involves adding a volatile salt to the tableting component to create pores in the tablet upon removal of the volatile component. This results in rapid disintegration when the tablet comes into contact with saliva. Common volatile salts used include camphor, ammonium bicarbonate, naphthalene, and urea. The tablets are then subjected to vacuum at 80 ºC for 30 minutes to remove the volatile components and create pores in the tablet.

**Advantages and disadvantages of Sublingual route [13]**

**Advantages**

Rapid absorption: The sublingual routes allow for fast absorption of drugs since they are placed directly in the mouth.

Drug stability: These routes of administration offer drug stability since the medication bypasses the acidic environment of the stomach where it may be degraded.

Avoidance of first-pass effect: Drugs that undergo first-pass metabolism can be administered via the sublingual route to avoid this effect.

**Disadvantages**

Inconvenient: The sublingual routes of administration may be inconvenient since the drug must be held in the mouth for a period of time.

Small doses: Due to the limited size of the oral cavity, smaller doses may be required for sublingual administration.

Unpleasant taste of some drugs: The taste of some drugs may be unpleasant when placed in the mouth, which can be problematic for patients.

**Ideal Characteristics of a drug to be selected [14,15]**

The drug being incorporated needs to have a taste that is pleasing to the patient.

The drug should have a low dosage requirement, preferably no more than 40mg.

It is preferable that the drug has a smaller or moderate molecular weight.

The drug should also possess good stability and solubility in both water and saliva.

For drugs used to treat addiction, it's ideal for them to have long half-lives that allow for less frequent dosing and slow metabolism into inactive metabolites.

The drug should be partially unionized at the pH of the oral cavity and have the ability to permeate oral mucosal tissue.

**Evaluation and characterization of Sublingual Delivery System**

**Physical Appearance and melting point**

Various organoleptic, physicochemical, and spectrophotometric methods are being used. It is found that the sample exhibits similar color, odor, taste, and texture as specified by the officials' pharmacopoeias.[16]

**Uniformity of Weight**

Weigh individually 20 units selected at random or, for single dose preparations in individual containers, the contents of 20 units, and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the table and none deviate by more than twice that percentage. [16-18]

Table

| Dosage form | Average weight | Percentage deviate |
|---|---|---|
| Uncoated and film coated tablets | 8o mg or less<br>More than 80 mg but less than 250 mg<br>250 mg or more | 10<br>7.5<br>5 |
| Capsules, granules and powders (single-dose) | Less than 300 mg | 10 |

**Wetting Time**
To measure Tablet WT, a modified version of the procedure reported is used. The tablet is positioned at the center of two layers of absorbent paper that are fitted into a rectangular plastic dish measuring 11 by 7.5 centimeters. The absorbent paper is wetted with distilled water and any excess water is drained out of the dish. Using a stopwatch, the time it takes for the water to diffuse from the wetted absorbent paper throughout the entire tablet is recorded.[18] Thin sections of porcine sublingual mucosa or skin are cut and mounted on glass slides. Excess PBS on the tissue surface is gently removed using filter paper. Contact angle measurements are performed at room temperature on a Krüss G2 angle meter by applying a standing drop of PBS from a 13 G needle on the tissue and measuring the contact angle for the sessile drop with manual baseline fitting using the Drop Shape Analysis software. [19-23]

**Drug entrapment efficiency**
To calculate the drug entrapment efficiency (DEE) of the film, the film with dimensions of 2 cm x 2 cm is dissolved in 20 ml of simulated salivary fluid with a pH of 6.8, while continuously shaking for 30 minutes. The solution is then analyzed using UV spectroscopy at a wavelength of 301 nm to determine the amount of drug present. [24]
% DEE:

$$\frac{\text{Total Amount of drug added} - \text{Amount of drug in } supernant}{Total\ amount\ of\ drug\ added} * 100$$

**Hardness**
The hardness of the tablets is determined using the hardness tester. To obtain the average hardness for each batch, ten tablets are selected at random and their hardness is measured.[25]

**Folding Endurance of film**
To determine the folding endurance of a film, manual repeated folding is performed at the same spot until the film breaks. This measures the film's flexibility and elasticity. For the prepared films, a 2x2 cm sample is taken and folded multiple times at the same location until it breaks. The number of times the film can be folded at the same location without breaking provides the exact value for the folding endurance.[26]

**Friability**
Ten tablets are taken and weighed collectively and placed in the friabilator chamber. In the friabilator, the tablets are exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. It is rotated for 100 rotations at a rate of 25 rpm. After 100 rotations the tablets are redusted and weighed collectively and % loss is calculated. [27]

**Disintegration**
In vitro disintegration time is being determined using a modified method. A disintegration tester is being used at 37±0.5°C with distilled water, and the tablet is being placed in a basket. The time it takes for the tablet to fully disintegrate into smaller particles is being recorded with a sample size of 5. For in vivo disintegration, the tablet is being placed on the floor of the mouth of 5 volunteers and the time it takes for complete disintegration in the mouth is being noted.[28] No official guideline is available for oral fast dissolving films. Pharmacopoeial disintegrating test apparatus may be used for this study. Typical disintegration time for film is 5-30 sec. [29] The tablet disintegration apparatus is being used to perform the test according to the European Pharmacopeia specifications for orodispersible films. Three (4 $cm^2$) film sections of each formula are being tested in phosphate buffer with pH 6.8 at 37°C. The time it takes for complete film disintegration, where no residue is left on the screen, is being recorded with a stop watch. Mean values are being calculated.[30]

***In-vitro* dispersion time**
10 tablets are being individually placed in 10 mL of phosphate buffer (pH=6.8) at 37°C±0.5 °C. The time it takes for complete dispersion is being determined.[31]

***In-vitro* swelling index**
The swelling rate of films is being evaluated by placing the film in a 2% (w/v) agar gel plate. The initial diameter of a 1x1 cm2 film is being determined in the agar gel plate and then it is being incubated at 37±1°C (D1).

At regular intervals (up to 1 h), the swollen film diameter is being re-measured (D2), and the swelling index is being calculated using the following formula. [32]

**Swelling index = D2-D1/D1**

**Drug Content (Assay) and Uniformity of content**

Assay of 10 units individually using an appropriate analytical method. Calculate the acceptance value. < 25 mg and <25% <of dose ratio of drug substance, content uniformity shall be performed as per assay method and ≥ 25 mg and ≥ 25% of dose ratio of drug substance, no need to perform content uniformity test, only assay shall be performed.[33]

**Dissolution Profile**

The in-vitro drug release study of NSD from the tablets is being carried out using USP dissolution test apparatus type-II Paddle Method in 900 ml of dissolution medium (phosphate buffer pH 6.8) at 37±0.5°C temperature and is being rotated at 60 rpm. A 5 ml aliquot of dissolution medium is withdrawn at specified time intervals and immediately replaced with an equal volume of fresh medium. Samples are suitably diluted and analyzed for percent drug release by using a UV spectrophotometer at λ = 238 nm. All the tests are being carried out in triplicate.[34]A volume of 2 mL of distilled water is being measured into the 15 mL glass funnel at 25°C, to be used as the dissolution medium. The tablet is placed into the dissolution medium undisturbed for each specified time, ranging from 15 to 120 s (stopwatch), to assess the dissolution profile of a representative formulation of E 40 mg SL tablets. Based on the initial results, the 60 and 120 s time-points are selected for subsequent experiments. At each appropriate time-point, the full vacuum is being applied by opening the on/off switch, causing the total volume of dissolution medium to be withdrawn instantly through a 0.45-µm filter membrane into the collection tube and terminating any further dissolution. The membrane prevents the passage of any undissolved particles and is replaced by a new membrane for each dissolution analysis.[35] To determine the dissolution profile of fast dissolving films, the experiment is being conducted using USP type II (paddle apparatus) with 300 mL of simulated salivary fluid (pH 6.8) as the dissolution medium, which is maintained at 37 ± 0.50C. The medium is stirred at 100 rpm. At every 30 sec interval, samples are being withdrawn and the same amount is being replaced with fresh medium. The amount of drug in the withdrawn samples is being determined by a UV spectrophotometer. The percent drug released is being plotted against time.[36]

**Permeability studies using porcine sublingual tissue**

Fresh sublingual tissues (floor of mouth) are being excised from white pigs (male, 50-100 kg), which are procured from a local slaughterhouse. The tissues are being stored in 0.15 M isotonic phosphate buffer at 4ºC immediately upon collection. All tissues are being used within 2 hours of procurement. The epithelial layer is being mechanically separated from the underlying connective tissue using surgical scissors. The integrity of porcine sublingual mucosa is being examined by measuring the permeability of four markers, namely [14C]-mannitol, [3H]-testosterone, [14C]-PEG4000, and [3H]-water using the method described below.

The permeation study is being conducted using a Side-Bi-Side diffusion chamber system. The diffusion area is 0.196 $cm^2$, and the volume for each chamber is 4 ml. The temperature of the system is being maintained at 37°C by continuous circulation of heated water in water jackets surrounding the chambers. The solution in each chamber is being stirred with magnetic bars. Each tissue is being mounted between the donor and receiver chambers of the diffusion cells with the surface of mucosa facing the donor chamber. After equilibration with isotonic phosphate buffer in both chambers at 37 ºC for 30 min, the receiver chamber and donor chamber are being filled with 4 ml pre-warmed phosphate buffer and testing solution, respectively. Samples of 200 µl are being withdrawn from the receiver chamber at pre-determined time intervals, and the concentration is being determined by the HPLC method. [37]

**Challenges and Future Prospective**

Advanced transmucosal delivery systems are being developed to administer new drugs through

the buccal mucosa. Clinical studies are testing the absorption of new chemical entities via this route while also investigating the efficacy of existing oral tablets when used as buccal, gingival, or sublingual dosage forms. Successful outcomes from these studies have resulted in the ongoing development of transmucosal dosage forms for a range of drugs including benzodiazepines, fentanyl, buprenorphine, morphine, and captopril.[38] While thin-film technology (TFT) is ideal for buccal or sublingual delivery, there are currently only limited APIs available as OTDD dosage forms. However, Midatech's nanoparticle-based insulin film was found safe in Phase I trials, with a Phase II trial planned for 2014. Films are made through casting or extrusion with polymer selection based on film thickness and drug compatibility. Dixit and Puthli's review covers materials, manufacturing, and applications of TFT in detail. [39] In recent years, there has been a growing interest in sublingual formulations, and as a result, an increasing number of sublingual products have been introduced to the market. This delivery method is applicable to a wide range of substances, including macromolecules, peptides, and proteins. Having appropriate in vitro and in vivo models is crucial when developing sublingual formulations. Despite their potential benefits, the clinical advantages of these formulations may not always be significant enough to convince regulatory agencies of their efficacy. Furthermore, there are potential risks associated with their use, such as accidental overdose, local irritation, and allergic reactions. Despite these concerns, sublingual formulations have not been extensively studied, and there is currently no specific guidance available for their development.[40]

**Recent Development**

A sublingual aerosol formulation called Nitrolingual spray has been developed to deliver nitroglycerine using a metered-dose spraying pump that contains propellants. This formulation allows for the rapid absorption and increased bioavailability of nitroglycerine when sprayed onto or under the tongue in the form of droplets, making it an effective option for treating hypertension when a quick onset of action is needed.[41] New bio-adhesive materials are gaining attention due to their ability not only to adhere well but also to bind specifically to certain cells. The emergence of such materials has led to the development of oral mucosal adhesion products with improved drug delivery. Sublingual and buccal routes offer a desirable constant release profile, but challenges remain, such as involuntary saliva secretion and foreign-body response, which limit drug absorption and patient compliance. Additionally, the choice of drugs is limited, and the use of penetration enhancers may impair mucus. Thus, further research is needed to find new materials and strategies to improve oral mucosal drug delivery.[42]

## 2. Conclusion

In conclusion, sublingual drug delivery is a promising alternative to traditional oral drug administration routes. The sublingual route offers a number of advantages, including rapid onset of action, avoidance of first-pass metabolism, and improved bioavailability. Sublingual drug delivery can be particularly beneficial for drugs that are poorly soluble or have low bioavailability when taken orally. Furthermore, the ease of administration and reduced risk of adverse effects make it an attractive option for patients who have difficulty swallowing or are unable to take medications orally.

While sublingual drug delivery has shown great potential, further research is needed to optimize the design and development of sublingual drug formulations. Future studies should focus on identifying the optimal drug candidates, optimizing formulation parameters such as the choice of excipients and the drug dosage, and evaluating the safety and efficacy of sublingual drug delivery in different patient populations. Overall, sublingual drug delivery has the potential to revolutionize the way we administer medications and improve patient outcomes.

**Authors' Contributions**

Ishwori Rawat and Meenakshi Kandwal conceived and designed the Project. Ishwori Rawat collected the literatures and wrote the manuscript. Shivananda Patil and Meenakshi Kandwal revised

the manuscript. All the authors have approved the manuscript for publication.

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Not applicable

## 3. Reference

1. Nibha KP, Pancholi SS. An overview on: Sublingual route for systemic drug delivery. Intra-oral Spray Technology. 2012:3.
2. Sattar M, Sayed OM, Lane ME. Oral transmucosal drug delivery–current status and future prospects. International journal of pharmaceutics. 2014 Aug 25;471(1-2):498-506.
3. Hassanali MZ, Houston DM, Heard C. Analysis of the oral delivery of vitamin D3 from BetterYouDLux spray formulations.2012:
4. Bhupinder B, Sarita J. Formulation and evaluation of fast dissolving sublingual films of Rizatriptan Benzoate. Int J Drug Dev Res. 2012 Jan;4(1):133-43.
5. Davies A, Mundin G, Vriens J, Webber K, Buchanan A, Waghorn M. The influence of low salivary flow rates on the absorption of a sublingual fentanyl citrate formulation for breakthrough cancer pain. Journal of Pain and Symptom Management. 2016.51(3):538-45.
6. Nayak BS, Sourajit S, Palo M, Behera S. Sublingual drug delivery system: a novel approach. Int. J. Pharm. Drug Anal. 2017;10(5):399-405.
7. Wang Z, Chow MS. Overview and appraisal of the current concept and technologies for improvement of sublingual drug delivery. Therapeutic delivery. 2014;5(7):807-16.
8. Saha PU, Verma SU, Das PS. Sublingual drug delivery: an indication of potential alternative route. International Journal of Current Pharmaceutical Research. 2017;9(6):5.
9. Bhati R, Nagrajan RK. A detailed review on oral mucosal drug delivery system. International Journal of Pharmaceutical Sciences and Research. 2012;3(3):659.
10. Hua S. Advances in nanoparticulate drug delivery approaches for sublingual and buccal administration. Frontiers in pharmacology. 2019;10:1328.
11. Patel P, Makwana S, Jobanputra U, Ravat M, Ajmera A, Patel M. Sublingual route for the systemic delivery of Ondansetron. Int J Drug Dev Res. 2011;3:36-44.
12. Khan AB, Kingsley T, Caroline P. Sublingual tablets and the benefits of the sublingual route of administration. Journal of Pharmaceutical Research. 2017;16(3):257-67.
13. Pawar PP, Ghorpade HS, Kokane BA. Sublingual route for systemic drug delivery. Journal of Drug Delivery and Therapeutics. 2018;8(6-s):340-3.
14. Das NG, Das SK. Development of mucoadhesive dosage forms of buprenorphine for sublingual drug delivery. Drug delivery. 2004;11(2):89-95.
15. Prabhu SC, Parsekar SD, Shetty A, Monteiro SS, Azharuddin M, Shabaraya AR. A review on fast dissolving sublingual films for systemic drug delivery. Int J Pharm Chem Sci. 2014;3(2):501-11.
16. Kumar D, Sharma A, Garg R. Formulation and Evaluation of Sublingual Tablet of Losartan Potassium. Asian Journal of Pharmaceutical Research and Development. 2018;6(4):54-66.
17. Indian pharmacopoeia. Vol. 1. India:Ministry of Health & Family Welfare: 2022. Uniformity of weight; p.308.
18. Pandey J, Khanal B, Bhandari J, Bashyal R, Pandey A, Mikrani AA, Aryal P, Bhandari R. Physicochemical evaluation of Diploknema butyracea seed extract and formulation of ketoconazole ointment by using the fat as a base. Journal of Food Quality. 2021;2021:1-1.
19. Dhakal B, Thakur JK, Mahato RK, Rawat I, Rabin DC, Chhetri RR, Shah KP, Adhikari A, Pandey J. Formulation of Ebastine Fast-Disintegrating Tablet Using Coprocessed Superdisintegrants and Evaluation of Quality Control Parameters. The Scientific World Journal. 2022;2022.
20. Acharya S, Pandey J, Joshi Hp, Parajuli G, Poudel N, Poudel S, Gurung S. Formulation and evaluation of gastro retentive floating

tablet of amlodipine besylate using natural organic polymers. Int J App Pharm. 2022;14(4):227-34.
21. Koirala S, Nepal P, Ghimire G, Basnet R, Rawat I, Dahal A, Pandey J, Parajuli-Baral K. Formulation and evaluation of mucoadhesive buccal tablets of aceclofenac. Heliyon. 2021;7(3):e06439.
22. Rawas-Qalaji MM, Simons FE, Simons KJ. Fast-disintegrating sublingual epinephrine tablets: effect of tablet dimensions on tablet characteristics. Drug development and industrial pharmacy. 2007;33(5):523-30.
23. Stie MB, Gätke JR, Wan F, Chronakis IS, Jacobsen J, Nielsen HM. Swelling of mucoadhesive electrospun chitosan/polyethylene oxide nanofibers facilitates adhesion to the sublingual mucosa. Carbohydrate polymers. 2020;242:116428.
24. Kalia V, Garg T, Rath G, Goyal AK. Development and evaluation of a sublingual film of the antiemetic granisetron hydrochloride. Artificial cells, nanomedicine, and biotechnology. 2016 ;44(3):842-6.
25. Aboutaleb AE, Abdel-Rahman SI, Ahmed MO, Younis MA. Design and evaluation of domperidone sublingual tablets. Int J Pharm Pharm Sci. 2016;8(6):195-201.
26. Gholve S, Savalsure S, Bhusnure O, Suryavanshi S, Birajdar M. Formulation and evaluation of oral fast dissolving sublingual film of propranolol HCl. International Journal of Pharma Research and Health Sciences. 2018;6(2):65-72.
27. Brahmbhatt H, Brahmbhatt H, Patel K, Makwana P, Chauhan N, Jain H, Upadhyay U. Formulation and Evaluation of Sublingual Tablet for Naratripta. Journal of Drug Delivery and Therapeutics. 2014;4(4):19-23.
28. Haarika BA, Veerareddy PR. Formulation and evaluation of fast disintegrating rizatriptan benzoate sublingual tablets. Malay J Pharm Sci. 2012;10(1):45-60.
29. Gholve S, Savalsure S, Bhusnure O, Suryavanshi S, Birajdar M. Formulation and evaluation of oral fast dissolving sublingual film of propranolol HCl. International Journal of Pharma Research and Health Sciences. 2018;6(2):65-72.
30. Sayed S, Ibrahim HK, Mohamed MI, El-Milligi MF. Fast-dissolving sublingual films of terbutaline sulfate: formulation and in vitro/in vivo evaluation. Molecular Pharmaceutics. 2013;10(8):2942-7.
31. Hosny KM, Mosli HA, Hassan AH. Soy polysaccharide as a novel superdisintegrant in sildenafil citrate sublingual tablets: preparation, characterization, and in vivo evaluation. Drug Design, Development and Therapy. 2015;9:465.
32. Maghsoodi M, Rahmani M, Ghavimi H, Montazam SH, Soltani S, Alami M, Salatin S, Jelvehgari M. Fast dissolving sublingual films containing sumatriptan alone and combined with methoclopramide: evaluation in vitro drug release and mucosal permeation.Pharmaceutical Sciences.2016:22:153-163.
33. The United States pharmacopeia.National formulary. Vol.4. Rockville(MD):United States Pharmacopeial Convention; 2020. Content Uniformity;p 7084.
34. Chatap VK, Maurya AR, Deshmukh PK, Zawar LR. Formulation and evaluation of nisoldipne sublingual tablets using pullulan & chitosan for rapid oromucosal absorption. Advances in Pharmacology and Pharmacy. 2013;1(1):18-25.
35. Rachid O, Rawas-Qalaji M, Simons FE, Simons KJ. Dissolution testing of sublingual tablets: a novel in vitro method. AAPS PharmSciTech. 2011;12:544-52.
36. Pather SI, Rathbone MJ, Şenel S. Current status and the future of buccal drug delivery systems. Expert Opinion on Drug Delivery. 2008;5(5):531-42.
37. Wang Y, Zuo Z, Lee KK, Chow MS. Evaluation of HO-1-u-1 cell line as an in vitro model for sublingual drug delivery involving passive diffusion—Initial validation studies. International journal of pharmaceutics. 2007 Apr 4;334(1-2):27-34.
38. Hoogstraate JA, Wertz PW. Drug delivery via the buccal mucosa. Pharmaceutical Science & Technology Today. 1998;1(7):309-16.
39. Sattar M, Sayed OM, Lane ME. Oral transmucosal drug delivery–current status and future prospects. International journal of pharmaceutics. 2014 ;471(1-2):498-506.

40. Sah S, Badola A, Kothiyal P. Sublingual tablets: an overview. Indian Journal of Pharmaceutical and Biological Research. 2016 Apr 1;4(2):20.
41. Narang N, Sharma J. Sublingual mucosa as a route for systemic drug delivery. Int J Pharm Pharm Sci. 2011;3(Suppl 2):18-22.
42. Guo YG, Singh AP. Emerging strategies for enhancing buccal and sublingual administration of nutraceuticals and pharamaceuticals. Journal of Drug Delivery Science and Technology. 2019;52:440-51.