International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 6 Issue 4, May-June 2022 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

Advancement in the Recently Development of Sublingual Tablet for Various Diseases: A Review

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ABSTRACT

The oral mucosa enables for rapid absorption and high bioavailability of drugs, as well as an early onset of pharmacological impact. Many oral mucosal delivery, on the other hand, are compromised because the active ingredient may be eaten before being released and absorbed locally into organic phenomenon. The main purpose was to investigate the creation of novel sublingual tablets for a variety of illnesses. During our investigation, we determined that all of the given sublingual tablets are made utilizing the direct compression method, and that the sublingual route is the best option in an emergency or for those who have difficulty in swallowing. All of the drugs have a considerable effect and offer excellent results.

KEYWORDS: *Sublingual Route, Sublingual tablet, Direct Compression, Bioavailability*

How to cite this paper: Meenakshi Verma | Pravin Kumar | Mahendra Singh Ashawat "Advancement in the Recently Development of Sublingual Tablet for Various Diseases: A Review" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-6 | Issue-4, June 2022, pp.483-489, URL: www.ijtsrd.com/papers/ijtsrd50046.pdf

IJTSRD50046

1. INTRODUCTION

[1.] Oral administration is a route of administration where a substance is taken through the oral cavity. Tablet is defined as a solid dosage form containing medicament with or without excipients. This is the most popular dosage form and 70% of the total medicines are dispensed in the form of tablet. Sublingual administration of a medicine indicates that the drug is placed under the tongue and enters the blood-stream directly through the ventral surface of the tongue and the floor of the oral cavity.

[2.] In this the drug, instantly diffuses into venous blood. The venous blood drains into a single trunk from the sublingual portion of the oral cavity, which subsequently drains into the superior vena cava via the internal jugular vein, the subclavian vein, and the brachiocephalic vein. As a result, unlike oral delivery, venous return from these locations enters the systemic circulation, bypassing pre-systemic drug clearance.
[3.] Young children, geriatric patients, mentally retarded and bedridden patients who used to suffer from dysphagia and hand tremors can benefit from tablets that disintegrate or dissolve quickly in the patient's mouth.

Drug which is absorbed from stomach goes to mesenteric circulation which connects through portal vein, thus the absorption through oral cavity avoids first pass metabolism. The sublingual tablets are usually small, flat and biconvex compressed lightly to keep them soft. The medicine must dissolve in a small amount of saliva; the patient should avoid eating, drinking, smoking, and possibly talking after inserting the tablet below the tongue to keep it in place.

[4.] Systemic drug delivery through the sublingual route had provided immediate onset of pharmacological action.

[5.] The medicine is absorbed more effectively through the sublingual route than through the oral route, and it is only transmitted through the body through hypodermic injection.
[6.] The majority of drugs which are administered

through sublingual route falls in the category of anti-anginal drug. Swallowing problems in children are prevalent due to their underdeveloped muscular and neurological systems, but they can be quickly remedied with the use of a fast-acting sublingual troche.

1.1. Sublingual glands

[7.] Sublingual glands, commonly known as salivary glands, are located beneath the tongue on the floor of the mouth. Mucin is produced by these glands, which aids in the formation of saliva. The interior of the mouth is kept lubricated by the gland secretions, which is important for chewing and swallowing food.

[8.] Absorption is defined as the transport of a drug from its administration site to the systemic circulation; hence, absorption is proportional to the thickness of the membrane layer. Mucosa thicknesses of 100, 200, 250, 500,600 micrometres are seen in the sublingual, buccal, gingival, and palatal regions, respectively. The sublingual route is capable of delivering a rapid beginning of effect due to its high permeability and rich blood supply, making it an excellent route for medications with a short delivery duration and a frequent dosage regimen. The medication is released into saliva, and its further distribution could result in the drug being absorbed throughout the oral cavity.

1.2. Sublingual absorption

Sublingual delivery, which literally means "under the tongue," is a method of administering chemicals through the mouth so that they are quickly absorbed through the blood vessels beneath the tongue rather than the digestive tract. Most sublingual chemicals are absorbed by simple diffusion, with the sublingual area functioning like litmus paper, rapidly soaking up the contents. However, not all substances are permeable and accessible to the mouth mucosa.

[9.] Glyceryl trinitrate, a powerful coronary vasodilator used for the quick symptomatic relief of angina, is one of the most well-known medications that is consistently used with remarkable success. When taken sublingually, it has been found to be quite effective, being pharmacologically active within only 1–2 minutes. The delivery of the drug as an aerosol spray resulted in quick symptom alleviation and first-class metabolism. When compared to the sublingual spray, the degree of first class metabolism dropped to 48 percent with sublingual tablets and 28 percent with the oral dose. Nitrate concentrations in plasma can be maintained for up to 24 hours after sublingual administration**.**

[10.] Following sublingual delivery of Verapamil (a calcium channel antagonist indicated for the treatment of angina, hypertension, and some supraventricular arrhythmias), the ventricular rate was well controlled.

1.3. Mechanics of sublingual absorption

[9,11.] The permeability of the solution (osmosis), ionisation (pH),molecular weight of the substances are all elements to consider when determining the oral mucosa's absorption capabilities. Absorption through the oral mucosa has been shown to increase when the carrier pH is lower (more acidic) and to decrease when the carrier pH is lower (less acidic) (more alkaline)

[12,13] The sublingual artery continues to nourish the gland beneath the tongue. The mucous membranes of the mouth, tongue, and gums are nourished by the gland and its branches. Two symmetrical branches meet and join at the tip of the jawbone and tongue. Another branch joins and anastomoses with the facial artery's submental branches. The sublingual artery is formed by the lingual artery, which arises from the external carotid artery and feeds blood to the tongue and the floor of the mouth. The internal carotid artery is close by, allowing quick access to its course, which supplies the majority of the cerebral hemisphere.

[14.] Endocytosis is the process of a cell being consumed by another (the uptake of particles by a cell as though by hollowly wrapping itself around it) is also capable of absorbing by the cells of the oral epithelium and epidermis. In most cases, the absorbed particles are too big to penetrate through the wall.. A mucous membrane lines the inside of the mouth, which is covered in squamous epithelium and contains mucous glands. The buccal mucosa tissue is comparable to the sublingual mucosa tissue.

1.4. Osmosis

[13.] A drug must be able to pass through the buccal mucous membranes via a diffusion process known as osmosis, which governs both intestinal and sublingual absorption, to be successfully absorbed sublingually. The osmotic difference in the blood between the intracellular and extracellular fluid affects the distribution of water across cell membranes.

Small particles that dissolve easily in water rarely cause problems with permeation and diffusion, allowing them to flow freely across the body's tissues. The chemicals are rapidly metabolised as a result of active translocation into cells. The molecules like glucose (fructose) and amino acids are essential for cell metabolism, and specialised procedures have evolved to let them quickly diffuse and penetrate across cell membranes.

1.5. Advantages[2,4]

- Quick onset of action is achieved as compared to the oral route.
- Low dosage improves efficacy while lowering the incidence of adverse effects.
- They can easily taken by oral cavity, without the need for water or chewing.
- Liver is bypassed and also drug is protected from degradation due due to digestive enzymes on the middle of GI tract.
- Patient compliance is increased because injections eliminate associated pain; pharmaceuticals are administered to unconscious or impaired patients; and delivery is more convenient than injections or oral medications.
- Quick absorption and blood levels are high due to high vascularization of the region and therefore particularly useful for administration of antianginal drugs.
- The oral cavity's large contact surface area allows for rapid and thorough medication absorption.
- Due to rapid action, these sublingual dosage forms are widely used in emergency conditions. For example. Asthma.

1.6. Disadvantages[2,4]

- Sublingual administration of drugs interferes with eating, drinking, and taking, this route is generally unsuitable for prolonged administration.
- Despite the fact that this method of medication administration is not well adapted to long-term delivery systems.
- Sublingual medication cannot be taken to those patients who are not cooperative.
- While taking sublingual medication, patients do not smoke sublingual medication, because smoking causes vasoconstriction of the vessels. This will decrease the absorption of the medication.
- Various types of sublingual dosage forms are available but most common forms are tablets, films and sprays are in trends these days. For the preparation of these dosage forms different methods are described according to their feasibility and advantages over.
- In any case, tooth staining and brought about by long term utilization of this technique with acidic or generally burning medications and fillers.

2. METHODS OF PREPARATION OF FAST DISSOLVING SUBLINGUAL TABLET

A. Direct Compression

[15.]The most cost-effective and simplest method of tablet production is direct compression. This approach can now be used to prepare fast dissolving tablet due the availability of better excipients, particularly superdisintegrant and sugar-based excipients. For heat labile medicines, this approach works well.

B. Freeze drying

[16.]Lyophilization is the process of drying at a low temperature under conditions where water is removed through sublimation. The drug is suspended in a water-soluble matrix, which is subsequently freeze-dried to create a porous structure. When lyophilized tablets are placed in the mouth, saliva immediately penetrates the pores and dissolves the tablets in less than 5 Heat-sensitive medications, also known as thermo-labile compounds, benefit from lyophilization.

C. Moulding

[17.]Moulded tablets are prepared using water-soluble components in this manner, allowing the tablets to dissolve entirely and quickly. The powder mixture is wet with a hydroalcoholic solvent before being moulded into tablets at a lower pressure than traditional tablet compression. After that, the solvent is removed by air drying. Molded tablets are substantially larger than compressed tablets. These have a permeable structure that helps in dissolution.

D. Mass Extrusion

[18.]In the mass extrusion technique, Using a solvent mixture of water soluble polyethylene glycol and methanol, a mixture of active drug and other ingredients is softened, and the softened mass is then extruded using a syringe or extruder to form a cylinder of product, which is then cut into even segments with heated blades to form tablets. The dried cylinder can be used to cover bitter-tasting medication granules, masking their unpleasant flavour.

E. Tablet Moulding

[19.]The solvent method and the heat method are the two types of moulding processes. Solvent-produced tablets are less compact than compressed tablets, and they have a porous structure that allows them to dissolve more quickly. The mechanical strength of moulded tablets is an issue that must be addressed. Binding agents must be corporated to increase the mechanical strength of the tablets. Spray congealing produces the masked drug particles, which adds to the flavour masking issue with this approach. As an active component, a lactose-based tablet triturate is made from a molten mixture of hydrogenated polyethylene glycol, cottonseed oil, lecithin, and sodium carbonate. When compared to lyophilization, the moulding method yields tablets that are simple to scale up for industrial makers.

F. Spray Drying

[20.]Spray drying can produce porous, little particles that disintegrate quickly. A particulate support matrix is used in this method, which is made by spray drying an aqueous composition containing the support matrix and other elements into a fine and porous powder. The mixture was then combined with active components and shaped into tablets. Hydrolyzed and non-hydrolyzed gelatins, mannitol as a bulking agent, and sodium starch glycolate are examples of supporting agents. To improve disintegration and dissolve, add crosscarmellose sodium with an acidic material as a dissolving agent. A tablet compacted from spray dried powder dissolved in 20 seconds when immersed in aqueous media.

3. NOVEL INVESTIGATIONS FOR SUBLINGUAL TABLETS FOR DIFFERENT DRUGS

In recent past other than anti anginal drugs, different other drug in form of tablets has been explored via sublingual route for different disease conditions.

A. Misoprostol

[21.]Shagufta parveen et.al work on this drug showed that the effectiveness and tolerability of misoprostol as cervical ripening agent in 1st trimester abortion by comparing different route of adminstration before surgical evacuation. A total of 150 randomly selected married women were separated into three groups for misoprostol single dose delivery by sublingual, vaginal, and oral routes. In the sublingual and vaginal groups, the medication was given3-4 hours before surgical evacuation, while in the oral group; it was given 12 hours before the surgery. The time it took for the ripening to complete, the dilatation obtained, the length of the procedure, intra-operative blood loss, and pain score were all used to determine efficacy. On the basis of side effects, tolerance was determined. The above details of data showed that as comparison to vaginal and oral methods, sublingual treatment took less time (3.7±1.2 hr) to complete cervical softening.

B. Glimepiride

[22.]Wafa Al-Madhagi investigated a new glimepiride compound for sublingual delivery and predict the evaluation parameter with physicochemical properties of drug. The five pill formulations were created by checking or altering the qualities of excipients, and it was eventually determined that formulation 5th was the most successful. After passing through filter number 60, the exact amount of the active component and all additives were homogeneously blended using geometric dilution, and finally magnesium stearate was added for lubrication and mixed well. In our study a micro press tablet punching machine was used to crush the blended material using an 8 mm standard concave punch. The total weight of formulations was accepted up to 150 mg. Two acceptable formulations of the new sublingual medication were created, but one of them had a disintegration time of 1.45 minutes, so they were looking for a better one.[1]The five formulations had a disintegration time of 21 seconds, indicating that glimiperide can be used as a sublingual tablet in an emergency and that hardness and weight variation were satisfactory. Formula 5 is the most effective and produced the best results of all the formulations. The new sublingual formulation demonstrated good breakdown with 21 seconds and accepted hardness as well as weight variation which is more favoured than other formula. The assay for the newer sublingual glimepiride is 103 %, which is a positive result that indicates that the formula worked and passed most quality control tests, indicating that it is suitable for marketing.

When compared to a simple tablet of glimeperide, the medicine is taken by mouth, absorbed from the GI tract, and transported to the liver via the portal vein within 1 hour, with peak drug levels occurring at 2-3 hours, showing first pass action. The medication has a low solubility because of poor water solubility and wetability make pharmaceutical formulations difficult and result in variable oral bioavailability, it's a good idea to turn it into a new dosage form.

C. Venlafaxine HCl

[23.]ChauhanVishakha et.al formulated a sublingual tablet of Venlafaxine HCl to treat depression and also investigate the physicochemical parameters, in-vitro drug release of drug. Each of the seven batches of sublingual tablets had different sodium starch glycolate and cross-povidone concentrations. The hardness of the tablets ranged between 2.6 and 3.4 kg/cm2, and their friability was within acceptable ranges. The results of post compression testing on wetting time, disintegration time, and content homogeneity are all positive. The maximum cumulative percentage drug release in 30 minutes was found in formulation F7, which was tested in vitro. Formulation 7 with crosspovidone (15mg) was shown to be the best in terms of drug release properties. The five formulations were completed after altering the binder to Flulac and aerosil with a disintegration time of 21 seconds and approved hardness as well as weight variation. A new product (subglimepiride) passed the test with a score of 103 percent, which is a good outcome.

As compiled with the oral route (immediate release and sustained release tablet), the drug release occurs and gives good action with prominent results as

extended for 12 hours, and zero order release was discovered as the mechanism of drug release. The release rate increases as the polymer fraction decreases, and formulations using a variety of dissolution techniques produce drug release patterns that are within acceptable ranges.

D. Sufentanil

[24.]Caitlin E Reardon et al. investigate that when Sufentanil Sublingual Tablet (SST) was compared to placebo in Phase III clinical trials, the summed pain intensity score decreased statistically significantly. The bioavailability of a single sublingual tablet was 52 % in our tests, but it dropped to 35 % after repeated doses.[17]

[25.]Sufentanil Dennis M Fisheret.al Ketoconazole (a CYP3A4 inhibitor) increased the maximum plasma concentration by 19% while also increasing the area under the curve by 77%. Within 30 minutes of a single 30-g dose, sufentanil plasma concentrations neared the established analgesic threshold, peaked at 1 hour, and then declined below therapeutic levels by 3 hours. Plasma concentrations had attained a plateau with hourly delivery by the sixth dose. The time it took for concentrations to drop 50% from their maximum after 1 treatment and 12 doses was identical. Clearance increased as people gained weight, decreased as they became older, and was unaffected by renal or hepatic illness.

[26.]Susanna Porela- Tiihonen et.al estimates that sublingual sufentanil nanotablets have been created; 15 mcg tablet for a patient-controlled analgesia device and 30-mcg tablet for a single-dose device supplied by a healthcare practitioner. A 15 mcg pill requires a minimum of 20 minutes between doses, with a treatment time of up to 72 hours. A single 30-mcg nano tablet has a one-hour dose duration. After the initial sublingual sufentanil tablet, the mean plasma elimination half-life is 13 hours, and bioavailability is 47-57 %.

Merja Kokki et.al demonstrated in our study that the new sublingual formulation offers significant advantages in the ambulatory setting, particularly in the face of social stigma and drug shortages related to the COVID-19 pandemic. Multiple hospital departments, including the emergency room and ambulatory surgery clinics, has studied and utilized sublingual sufentanil tablets. The use of a sublingual sufentanil tablet in a number of hospital departments, including the emergency room and ambulatory surgery clinics.

According to the findings of all investigations, it is a safe and dependable alternative to intravenous sedation for patients who require analgesia. It is a suitable analgesia alternative for chronic pain patients undergoing outpatient interventional treatments. In the face of COVID-19-related drug shortages and social isolation, physicians must develop innovative techniques to ensure patient comfort during interventional operations.[27.]SST is a sublingual analgesic that does not require the use of an IV and it is a sublingual analgesic that does not require the use of an IV. In the absence of the COVID-19 social distance requirement and drug shortages, this tablet offers a safe and dependable alternative to IV sedation that require analgesia. When parenteral opioids are in short supply, it may be a viable choice for adequate analgesia.

In comparison to other routes, the sublingual route is advantageous for patients because it shows a rapid onset of action with a lower dose and bypasses first pass metabolism, making it preferable in an emergency. Orally, the action is delayed and they show first pass metabolism, restricting the drug from reaching blood circulation.

E. Cyclobenzaprin

[28.]Haidar Majid et.al showed in their study to assess the development of the sublingual formulation of cyclobenzaprine, a promising agent for the treatment of psychological disorders. In our study they determine the preformulation parameters, invitro drug release, evaluation parameters of the drug and ex-vivo permeation studies. It was possible to examine the influence of dosage form changes under stress settings conditions, with the finding of a 33.85% decreased permeability due to salt disproportion. They predict in their study that by integrating the coherent processes of disintegration, dissolution, permeation, and metabolization within a physiological study design, the model enabled successful formulation development for cyclobenzaprine sublingual tablets and targeted development of patient-oriented oral cavity drugs.

As compared with other routs Sublingually, tablet is placed just under your tongue to dissolve and absorb into your blood through the tissue and gives quick onset of action (4-5 minutes) with least side effects so we can use in it with emergency or other main point is that the drug are absorbed under the tongue or between the cheek and gum can be easier to take for people who have problems in swallowing pills. They bypassing the digestive tract and first-pass metabolism allows for dose reduction which facilitates patient safety and adherence by reducing the risk of side effects.

F. Desmopressin Acetate

[29.]Natasha Alford et al. formulate a sublingual tablet for ant diuretic and investigate the evaluation

parameters with physicochemical properties of drug. The main active ingredient is desmopressin acetate and inactive ingredient is gelatin, NF (fish source), mannitol and anhydrous citric acid. The tablets are available in two strengths. Desmopressin acetate is found in each sublingual tablet in amounts of 27.7 mcg or 55.3 mcg. Women is 27.7 mcg once daily, one hour before bedtime, administered sublingually without water while men is 55.3 mcg once daily, one hour before bedtime, administered sublingually without water. They demonstrated that in few days a new lower dose sublingual tablet formulation that optimizes the balance between efficacy and tolerability was approved for symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in adults of any age with regular serum monitoring**.**

4. CONCLUSION

Sublingual drug delivery has been used to define a variety of medications with the goal of achieving rapid medication discharge and activity onset. Sublingual items were produces to defeat the trouble in gulping ordinary tablet, among paediatric, geriatric furthermore, psychiatric patients with dysphasia. Compared to regularly utilized tablets, cases and other oral measurement shapes, sublingual absorption is by and larger more quicker and more effective. Therefore sublingual, tablets are an accepted technology for systemic delivery of drugs.

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