"SUBLINGUAL DRUG DELIVERY SYSTEM"

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Abstract

The purpose of the study was to develop and enhance a sublingual pill for the therapy. It offers a number of advantages, including a quick onset of action and the capacity to bypass the liver. Sublingual pills are a quick and easy way to get your medication. The use of super disintegrates by direct compression was the major technology used in the creation of the Sublingual tablet. Oral mucosal medication administration is a potentially beneficial method of systemic drug delivery. Sublingual means "under the tongue" with inside the literal sense. As a result, the method comprises taking the medication orally and allowing it to be absorbed through blood vessels (systemic) situated beneath the tongue. A sublingual tablet is one that dissolves or disintegrates in the oral cavity without the need for water. Sublingual pills have traditionally been used to boost the solubility and bioavailability of water-soluble medications. Physiochemical characteristics such as melting point, solubility, partition coefficient, UV and FTIR tests were employed in the preformulation investigations. A UV spectroscopic method for quantitative drug estimation was developed. The tablets were made using the direct compression approach. The post compression studies were used to evaluate the product's quality, which comprised shape, size, weight fluctuation, hardness, friability, and wetting time PubMed and other standard sources were used to research and construct an overview of sublingual tablets and the advantages of the sublingual mode of administration. When compared to traditional dose forms, sublingual tablets were shown to have superior properties. Because of their quick breakdown, sublingually given tablets had higher bioavailability, a faster start of action, and improved dissolving characteristics. The use of super-disintegrants aided in fast disintegration, and this method can be utilised to treat acute diseases or emergency situations. Sublingual tablets or any other sublingual dose form can be employed to produce a faster onset of action, improved patient compliance, and higher bioavailability. Sublingual delivery is appropriate for medicines that undergo considerable first pass metabolism or degradation in the GIT. When compared to normal oral tablets, drugs delivered sublingually have higher bioavailability, which correlates to dosage reduction.

Keyword: Easy self-medication, Fast disintegration, Increased bioavailability, Sublingual tablet.

1.INTRODUCTION

Oral disintegrating tablets are a new form of tablet that dissolves quickly in saliva. Their unique features, such as the ability to administer them without the need of water, anyplace, and at any time, make them ideal for geriatric and paediatric patients. Patient compliance, quick beginning of action, enhanced bioavailability, and high stability are all advantages. Oral disintegrating tablets are also known as melt-in-mouth tablets, rapid melts, porous tablets, orodispersible tablets, quick dissolving tablets, and rapidly disintegrating pills(Nayak et al., 2018). FDTs are manufactured using a variety of methods, the most common of which being direct compression, lyophilization, and moulding. Super disintegrants are added to medicine formulations to aid in the break-up or disintegration of tablets into tiny particles that dissolve more quickly than if disintegrants are not present(Nayak et al., 2018). Other suitable oral cavity targeted areas include the pharynx, larynx, adenoids, and tonsils. Sublingual administration may be a more appealing alternate path of administration. The benefit of sublingual medication administration is that the medicine can be absorbed directly into the systemic circulation, skipping enzyme breakdown in the stomach

and liver. Furthermore, the thin sublingual mucosa (approximately 190 m compared to 500–800 m of buccal mucosa) and abundant blood supply in the sublingual area allow for efficient drug penetration (absorption) to produce high plasma drug concentration with a quick start of action. Nitroglycerin, which is used to treat acute angina, is a well-known example(Kumar Damit, Sharma Amit, 2018) .Dysphagia (difficulty swallowing) is a frequent condition in people of all ages, but it is most common in the elderly, children, and patients who are intellectually retarded, uncooperative, nauseous, or on restricted liquid intake/diets. Sublingual administration of the medicine entails placing the drug beneath the tongue, where it enters the bloodstream directly through the ventral surface of the tongue and the floor of the mouth(Kumar Damit, Sharma Amit, 2018).

2. OVERVIEW OF ORAL MUCOSA

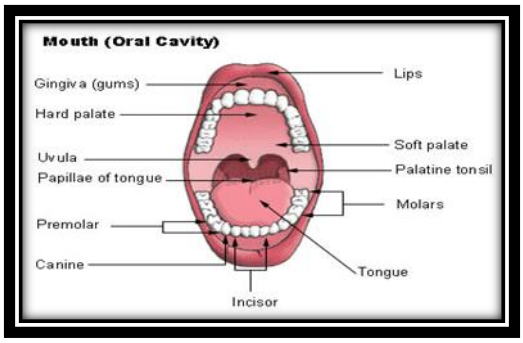

Fig-01 Oral Cavity

The oral cavity is divided into four zones where medications can be absorbed. the sublingual, buccal, gingival, and palate areas. The mucosal lining is divided into three different layers. The epithelial membrane, formed of stratified squamous epithelial cells, forms the outermost layer and serves as a protective barrier. The basement membrane is the epithelial membrane's deepest layer. The lamina propria is found underneath the epithelium, followed by the submucosa. The lamina propria is a connective tissue layer made of collagen and elastic fibres that is moist and less thick. The oral submucosa is densely packed with blood vessels(Bhati & Nagrajan, 2012). The oral cavity has three types of oral mucosa: lining mucosa, buccal mucosa, and sublingual mucosa (floor of the mouth). The specialised mucosa is located on the tongue's dorsal surface, whereas the masticatory mucosa is located on the hard palate (the top surface of the mouth) and the gingiva (gums). In an adult human, the lining mucosa accounts for around 60% of the total surface area of the oral mucosal lining, the masticatory mucosa for 25%, and the specialised mucosa for 15%. The masticatory mucosa is found in areas that are particularly vulnerable to the stress and strains caused by mastication(Kumar Damit, Sharma Amit, 2018).

Following absorption via the sublingual mucous membrane, the medication directly diffuses into the venous circulation, which drains directly into the superior vena cava through the internal jugular vein, subclavian vein, and brachiocephalic vein via a general trunk. In contrast to oral treatment, the venous return from these areas reaches the systemic circulation, bypassing hepatic metabolism. The direct flow of the medicine into the systemic circulation results in improved drug bioavailability and a rapid onset of therapeutic efficacy(Khan et al., 2017).

2.1 Drug Absorbed Through Oral Route

The salivary pH ranges from 5.5 to 7.0, and the saliva contains mucus as well as enzymes such as amylase and carboxylesterase, forming a cohesive gelatinous layer over all surfaces of the mouth cavity. The cohesiveness of the sublingual membrane causes mucoadhesion, which leads to medication absorption. The sublingual epithelial membrane is non-keratinized and 100-200m thick(Harris & Robinson, 1992). The presence of cholesterol, cholesterol esters, and glucosyl ceramides in the epithelial cells of the sublingual membrane makes it permeable to drug absorption, in contrast to other parts of the oral cavity. Because of the enhanced blood supply, as well as the relative thinness and high permeability of the sublingual mucosa, some medications can be absorbed quickly and have a higher bioavailability following sublingual administration. As a result, the sublingual area is an excellent location for attaining clinically effective medication concentrations in a short period of time when a quick beginning of action is required(Bayrak et al., 2011).

The sublingual area is continually cleansed by saliva and tongue movements, making it unsuitable for long-term dosage form retention.

2.2 Commercially Avilable Tablet In market

In recent years, just a few sublingual tablets for pharmacological delivery have been commercially accessible. These medications are used to treat angina, hypertension, cancer pain, migraines, and other conditions. Table 1 contains a list of commercially available authorised sublingual pills(Harris & Robinson, 1992).

Active ingredient	Brand name	Manufacturer
Asenapine	Saphris	Merck
Buprenorphine hydrochloride	Subutex	Sun pharma
Ergoloid mesylates	Ergomes	Cipla
Ergotamine tartrate	Ergomar	Rosedale pharmaceuticals
Fentanyl citrate	Abstral	Galena Biopharmaceuticals
Isosorbide dinitrate	Imdur	Astrazeneca
Nitroglycerin	Nitrostat	Pfizer
Zolpidem tartrate	Intermezzo	Purdue pharma

Table.01 list of commercially available authorised sublingual pills.

3. POTENTIAL DRUG CANDIDATE FOR SUBLINGUAL DELIVERY

There are several studies in the literature that show that when medications are delivered sublingually, their potency is increased. However, sublingual administration's promise for medication delivery has yet to be commercialised(Khan et al., 2017). According to a comparative efficacy trial of sublingual captopril, nifedipine, and prazosin, sublingual captopril may be a preferable option to sublingual nifedipine in treating hypertension situations owing to less adverse effects(Fort et al., 1994). Sublingual delivery of verapamil resulted in a significantly higher plasma concentration of the medication (C), a quicker absorption max rate, and higher bioavailability when compared to oral treatment. It was also proven to generate a quick and considerable decrease in ventricular rate.(Fort et al., 1994) When delivered sublingually rather than orally, the medication furosemide demonstrated a therapeutic benefit(McIntyre et al., 2005). Midazolam given sublingually was shown to be more efficient than diazepam given recall in the emergency management of acute febrile and afebrile (epileptic) convulsions in children(Fudala et al., 2003) Because of the beneficial outcomes revealed by sublingual tablets of buprenorphine and naloxone in the treatment of opiate addiction, a research study advocated office-based treatment of opiate addiction employing sublingual delivery of buprenorphine and naloxone.(Bayrak et al., 2011)

A sublingual zolmitriptan formulation was found to be very effective for the treatment of migraine and cluster headaches, with a quicker rate of absorption and greater drug exposure than subcutaneous injection(Supervía et al., 1998). 40mg of sublingually given piroxicam was shown to be equally efficacious as a 75 mg intramuscular injection of diclofenac in the emergency treatment of acute renal coli in
a randomised, double-blind clinical research investigation. (Rawas-Qalaji et al., 2006) A study advocated sublingual epinephrine as an alternative to self-injected epinephrine for the treatment of anaphylaxis because sublingually delivered epinephrine resulted in faster drug absorption and a greater peak plasma concentration in animal models when compared to self-injected epinephrine.(Gu et al., 2002) Estrogens have been proven in menopausal women with cardiovascular disease to promote coronary and peripheral vasodilation, vascular resistance reduction, and endothelial function improvement. Sublingual oestrogen administration has been proven to result in quicker drug absorption (i.e., shorter T higher C) than orally administration.(Volterrani et al., 1995) Preclinical research on vaccinations have indicated that sublingual vaccines can be highly immunogenic and may protect against the influenza virus and Helicobacter pylori.(Price et al., 1997)

Sublingual tablet formulation development

It is critical to examine the mechanism of a drug's absorption, physicochemical features, the role of the excipient utilised in formulation creation, taste masking strategies employed, and other factors when developing an appropriate sublingual tablet formulation.(Pedersen et al., 2011)

3.1 Mechanism Of Drug Absorption From The Sublingual Region

The medicine is absorbed through Passive diffusion, Active transport, or Endocytosis after sublingual delivery of a dosage form.(Song et al., 2008)Passive diffusion is an ad hoc method. The rate of drug diffusion into tissues is determined by molecular weight, drug solubility, concentration gradient, temperature, membrane surface area, and the closeness of the drug molecule to the membrane(Raghavan et al., 2010). When a medication molecule is unionised in the saliva, it is absorbed by passive diffusion. Several physical models have been depicted to describe the mechanism of drug absorption from saliva straight into the systemic circulation via the lipid bilayer of the mucous membrane. The partition coefficient of a medicine is directly connected to the rate of absorption across the mucosal membrane. Some amino acids, including as glutamic acid, L-ascorbic acid, nicotinic acid, and thiamine, are transported via a carrier-mediated pathway(Tayel et al., 2010). Lipids found in the sublingual mucous membrane serve as the primary barrier to the penetration of hydrophilic medicines. However, well-hydrated connective tissues give resistance to hydrophobic drug compounds. As a result, the possible transport channel across the sublingual mucous membrane might be either polar or non-polar. Polar molecules flow via the ionic channels found in the intercellular gaps of the epithelium or the aqueous pores present in the epithelial cells, whereas non-polar molecules pass through the lipid sections of the epithelium.(BECKETT et al., 1968)

4. PHYSICOCHEMICAL PROPERTIES OF THE DRUG

The physicochemical qualities of the medications allow passive diffusion over the sublingual membrane, which aids absorption.Table below lists the physicochemical parameters of various commercially available pharmaceuticals that are delivered sublingually.
For optimal absorption via the sublingual membrane, the medicine must be lipophilic enough to partition through the lipid bilayer but not so lipophilic that it cannot partition out once it is in the lipid bilayer(Vora et al., 1972). Oral medication absorption has been found to be satisfactory across a wide range of log P (octanol/water partition coefficient) values ranging from 1 to 5. When the log P value exceeds 5, the medication's salivary solubility is typically insufficient to give an appropriate concentration for the drug to diffuse across the lipid bilayer. The flux through the lipid bilayer is exactly proportional to the concentration gradient according to the diffusive model of absorption. As a result, decreased salivary solubility leads to decreased absorption rates and vice versa. To promote diffusion, a medication designed for sublingual administration should preferably have a molecular weight of less than 500 (as 29 free base(Vora et al., 1972) Because pharmaceuticals diffuse across the lipid bilayer in a unionised state, according to the pH-partition hypothesis, the pK of medications also plays a significant role in drug transport through the sublingual membrane. Unlike the gastrointestinal system, the oral cavity has a restricted pH range that ranges from 5.0 to 7.0. As a result, when a basic medicine is supplied in its salt form, it largely resides as a free unionised base if the pH is raised over its pKa value, and this increase in the unionised

Drug	Molecular weight	Largest dose	Water solubility	pK	Log p
Asenapine maleate	285.5	10 mg	3.7 mg/ml	8.6	4.9
Buprenorphine	467.6	10 mg	Insoluble in water	8.24, 10.0	4.9
Ergotamine tartrate	583.68	2mg	Insoluble in water	6.3	2.4
Fentanyl citrate	336	0.8 mg	0.025 mg/ml (citrate)	8.4	2.9
Nicotine	162.234	4mg	Slightly soluble	8.21	0.99
Nitroglycerin	227	0.6mg	1.8 mg/ml	-5.6	0.94

fraction of the drug significantly enhances its bioavailability.(BECKETT et al., 1968) As a result, the addition of a suitable buffer during the formulation of an ionizable medicine allows the pH of aqueous saliva to be controlled in a range most ideal for the optimum absorption of such pharmaceuticals. Changes in pH have no effect on medicines that lack ionizable groups. Because the absorptive area of the mouth cavity is substantially less than that of the gastrointestinal system, 31 high dosages cannot be supplied by this route. As a result, only powerful medications that require modest dosages to provide the intended therapeutic impact can be supplied via this method. In addition to these key medication characteristics, it is very desired that pharmaceuticals designed for sublingual administration be suitably flavour disguised in order to promote patient compliance(Sadoogh-Abasian & Evered, 1979).

5. FUNCTIONS OF EXCIPIENT USED

The amount and kind of disintegrants employed during formulation are also important in ensuring fast disintegration. To promote disintegration, effervescent agents are utilised. Water soluble excipients, such as saccharides, aid in quick disintegration by improving the wettability of the tablet matrix. However, the manufacturing process and some essential process characteristics might also have an impact on sublingual tablet disintegration and dissolving(Rathbone & Hadgraft, 1991).

Taste masking:-

Some medications may have an unpleasant or bitter taste. When such medications are dissolved in saliva for mucosal absorption, they may interact with taste buds in the tongue, producing a bitter and unpleasant flavour that patients may find unpalatable. Various physicochemical techniques that prevent the medicine from interacting with the taste buds and therefore eliminating the unpleasant sensory response increase patient acceptance of a formulation(Sadoogh-Abasian & Evered, 1979). Sweeteners, flavours, and other taste-masking agents are required ingredients in formulations containing medications with a disagreeable taste. Excipients based on sugar dissolve fast in saliva and generate endothermic heat of dissolution. They produce a pleasant taste in the tongue and are best suited for sublingual tablets in combination with other tastes. For medications that are to be dissolved in saliva, bitter drug coating is not an option(Roy & Flynn, 1989). To address this essential patient compliance issue, appropriate taste-masking solutions should be researched and included into product design throughout the formulation development stage. The electronic tongue, assessment of the frog taste nerve response, the spectrophotometric approach, and a human taste panel are among the technologies used to evaluate taste that have been published in the literature.(Bredenberg et al., 2003)

6. CHARACTERISTICS OF SUBLINGUAL TABLETS

Because of the brief residence period in the mouth, rapid disintegration and dissolution is critical for drug absorption following sublingual delivery. As a result, sublingual tablet formulations must be constructed in such a manner that they breakdown and dissolve quickly in saliva, without the use of any extra water(Riahi et al., 2008). A tablet's physical and mechanical properties, such as size, hardness, porosity, and wettability, all have an important impact in its disintegration time. A smaller tablet with low hardness and high porosity disintegrates faster than a bigger or harder tablet(Gu et al., 2002). A tablet that is very porous and has a low hardness, on the other hand, is more friable and prone to self-disintegration, which causes issues. During packing and transportation All techniques to increasing the mechanical strength of sublingual tablets should be investigated during formulation development, without affecting the sublingual tablet's disintegration and dissolve qualities.(Jacobson et al., 2013) Following sublingual delivery, the patient is recommended to avoid swallowing the pill and to refrain from eating, drinking, or chewing in order to promote medication absorption through the sublingual membrane. Even swallowing saliva should be avoided in order to avoid ingestion through the gastrointestinal system, where medication absorption may be ineffective or the medicine may degrade. Because these features cause some difficulty to the patient, they should be considered throughout the formulation development stage to promote patient compliance(Al-Ghananeem et al., 2006). Sublingual pills improve quick absorption and bioavailability, as well as a rapid commencement of action. If the medication is not completely dissolved, the

contact time with the sublingual membrane is too short, and/or permeability is too low, a portion of the formulation may be ingested and therefore not absorbed via the sublingual membrane, affecting the drug's bioavailability. Many sublingual pills may be jeopardised if the patient swallows the active medicinal component before it is released and absorbed via the sublingual membrane into the systemic circulation.(Khan et al., 2017) A sublingual tablet is intended to increase the retention of the active medicinal component beneath the tongue, prevent its swallowing, and limit inter and intra individual variability. This method employed a formula that included ordered mixes of fine active component particles and bioadhesive polymers coupled to coarser excipient carrier particles(Tayel et al., 2010). Tablets prepared in the manner described above have the ability to rapidly dissolve and release the medication, which adheres to the sublingual mucosa and therefore extends the contact time at the absorption site. The development of directly compressible sublingual tablets employing this method resulted in bio-adhesive retention of the active pharmaceutical component in the oral cavity and appropriate exposure of the medication to salivary fluid in the mouth, resulting in complete and quick sublingual absorption.(Roy & Flynn, 1989)

7. MANUFACTURING TECHNIQUES USED IN SUBLINGUAL TABLET FORMULATION

For commercial production of sublingual tablets, the direct compression technique is most widely utilised. It is a simple, cost-effective, and efficient method since it uses materials that may be properly combined and do not require further granulation stages before lubrication and compression. Direct compression sublingual tablets have a high mechanical strength and disintegrate quickly(Jacobson et al., 2013). Excipients that are both directly compressible and water soluble, as well as a super disintegrant and lubricants, are used in the formulation of the directly compressible sublingual tablet. Microcrystalline cellulose, a dry binder, buffers, surface-active chemicals, sweeteners, and flavours may also be included. Sugar-based excipients are commonly employed as bulking agents due to their high water solubility, sweetness, pleasant mouthfeel, and flavour masking properties.(Gu et al., 2002) Almost all sublingual preparations contain some saccharide-based components. The selection of a specific disintegrant and its amount are crucial for obtaining rapid disintegration and dissolution rates. If necessary during formulation development, effervescent compounds are utilised to improve the disintegration and dissolve rates of some sublingual tablet formulations.(Jacobson et al., 2013) In the literature, several unique ways of combining super disintegrants and other soluble and/or insoluble excipients to achieve quick dissolving and appropriate 47 mechanical strength have been published(Bredenberg et al., 2003). Flashtab technology with multiparticulate actives (coated crystals and uncoated or coated microgranules) is one example. The simultaneous presence of a disintegrant with a high swelling or disintegrating force (starch, cellulose, and direct-compression sugar), defined as "disintegrating agent," and a substance with a low swelling force (starch, cellulose, and direct-compression sugar), defined as "swelling agent," in these sublingual tablet formulations, was claimed to be the key factor in achieving rapid disintegration of the formulation. This technology's tablet has been reported to have appropriate mechanical strength(Bredenberg & Nyström, 2010). Daiichi (Tokyo, Japan) created a moderate-strength quick dissolving formulation by combining starch or cellulose with one or more water-soluble saccharides. Erythritol was discovered to be the optimum sugar for this type of formulation, exhibiting quick disintegration that was unaffected by tablet hardness, acceptable palatability with sweetening, and a refreshing feeling in the mouth due to the occurrence of endothermic heat of breakdown.(Harris & Robinson, 1992)

Compression molding

Tablets made by the compression moulding method disintegrate and dissolve quickly, generally within 5–10 seconds. These compositions provide unique issues during handling and packing; due to their low mechanical strength, they may necessitate specific packaging for transportation purposes(Dobetti, 2000). Alternatively, applying an appropriate binder can boost the mechanical strength of the compositions. The degree of binder, on the other hand, should be adjusted to minimise any negative effects on formulation disintegration and dissolution.

Compression moulding formulations often include soluble excipients to provide quick and thorough

dissolving, as well as taste modifiers to increase patient compliance. Molded tablets can also be made directly from a molten matrix in which the drug is dissolved or disseminated (heat moulding) or by evaporating the solvent from a drug solution or suspension at normal room pressure , a process known as no vacuum lyophilization(Dobetti, 2000).

There are also many patented processes available for the commercial fabrication of 53 compression moulded sublingual tablet compositions.

Novartis Consumer Health (Basel, Switzerland) has submitted a patent application for tablets made by distributing the medication solution or suspension into moulds, draining the solvent from the moulds using low-pressure heating or microwave radiation, and then sealing the dry units directly 55 in the mould(Dong et al., 2012). Nippon Shinyaku (Kyoto, Japan) compression molded and dried a drug-containing kneaded material. This technique claimed to give the tablet appropriate physicochemical stability, a pleasant look, and a dissolving period of less than 30 seconds in the sublingual 56 region.(Roy & Flynn, 1989)

Freeze drying:-

Freeze drying (lyophilization) is a costly and time-consuming procedure that results in tablets with low mechanical strength. Because of these factors, it is not a regularly utilised process for producing sublingual tablets. It does, however, offer certain advantages over other procedures in that the tablets produced by this process have a high porosity and disintegrate and dissolve immediately when placed under the tongue. It is a preferred method for compounds that are either unstable in nature or thermolabile(Fort et al., 1994). The lyophilization method entails decreasing the temperature of the medicine in an aqueous medium to below freezing, followed by the introduction of a high-pressure vacuum. During the drying process, a progressive temperature rise is applied to remove the water in the form of vapour, which is collected as ice on a condenser(Bayrak et al., 2011). The temperature of the product at the ice sublimation interface and the temperature during formulation collapse are crucial in order to get a freeze-dried cake of the medicine with optimal specifications. This method aids in the retention of the physical structure and the preservation of the substance during storage or transit.(Price et al., 1997) The resultant formulations are light in weight and have extremely porous architectures, allowing for quick dissolution or disintegration. The freeze-drying method may produce a product with an anamorphous structure, resulting in a faster dissolving rate. Tablets made utilising the freeze drying procedure, on the other hand, have poor stability at high temperatures and humidity levels of 60%(Khan et al., 2017). A uniform and consistent mixing of numerous formulation materials is essential in the creation of pharmaceutical formulations. A twin screw extruder is used in the production of pharmaceutical formulations that require homogeneous and consistent mixing of multiple formulation ingredients because the rotation of the intermeshing screws provides better mixing to produce a homogeneous solid containing finely dispersed drug particles or a solid-solution of drug in polymer(Khan et al., 2017). This can increase the dissolving rate and bioavailability of medication formulations that are weakly water soluble. A uniformly distributed active pharmaceutical component is also required for the manufacturing of drug-eluting devices with drug-release kinetics repeatability intra and inter-batch(Khan et al., 2017). Melting is performed by frictional heating within the barrel, and for twin-screw extruders, through shearing between the revolving screws and the barrel wall as the materials are transported. The barrel can also be heated or cooled using heaters installed on the barrel. The temperatures in the barrel portion are normally adjusted such that the viscosity of the melt is low enough to enable conveyance down the barrel and appropriate mixing while maintaining temperatures low enough to minimise thermal damage of the material(Raghavan et al., 2010) A twin screw extruder's screws are often designed to give various sorts of mixing and conveying conditions at different zones in the barrel(Al-Ghananeem et al., 2006). Modular screws with various parts placed on a common shaft enable for the customising and optimization of the screw design for each product during product development. Based on the parameters of the 65 process, sections of the screw can be constructed to perform particle-size reduction and conveying operations. However, hot melt extrusion is not a practical procedure for the formulation of thermolabile active medicinal components in sublingual tablet dosage forms.(McIntyre et al., 2005)

8. CONCLUSION

This research demonstrates that there are a variety of commercially available sublingual formulations made utilising diverse methods. According to the information that is publically accessible about sublingual tablets, this specific dosage form has a very excellent potential to improve medication delivery for the treatment of a variety of illnesses. Sublingual dose forms have been found in most reported cases and research studies to not only enhance patient compliance, but also to minimise the time for initiation of therapeutic response and significantly boost drug bioavailability when compared to standard orally delivered tablets.

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