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SUBLINGUAL DRUG DELIVERY SYSTEM AND ITS FUTURE PROSPECTIVE: AN OVERVIEW OF FORMULATION AND TECHNOLOGY

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Abstract:

Novel drug delivery system assists to achieve better patient compliance. Sublingual tablets are one of them. Drug delivery via the oral mucous membrane is considered to be a promising alternative to the oral route. Sublingual literally meaning is "under the tongue", refers to a method of administrating substance via mouth in such a way that the substance is rapidly absorbed via blood vessels under tongue. Due to rapid onset of action, ease of administration, versatility, painless and paramount patient compliance oral administration is considered as most satisfactory route for the administration of drug.

Keywords: *Sublingual tablet, Superdisintegrants, Crospovidone, Croscarmellose Sodium, Sodium Starch Glycolate*

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1.INTRODUCTION:

Sublingual route of administration means placing the drug under the tongue. For sublingual administration patient has to, **place the tablet under your tongue and wait until it dissolves.** The sublingual route bypasses the first-pass metabolism and hence facilitates rapid absorption of the drug into the systemic circulation. Drug directly reaches the systemic circulation using blood vessels. Many drugs are absorbed through sublingual administration, including **cardiovascular drugs, steroids, barbiturates, benzodiazepines, Opioid analgesics, THC, CBD, some proteins and increasingly, vitamins and minerals**. Medically, 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.[1]

1.1 REQUIREMENTS OF SUBLINGUAL DOSAGE FORM

- Rate of absorption from the saliva solution
- Drug and dosage form stability
- Mechanical strength of final product
- Taste, mouth feel, swallowing ability
- Exhibit low sensitivity to environmental conditions such as humidity and temperature
- Allows the manufacture of tablet using conventional processing and packaging equipment at low cost
- Overall bioavailability
- Require no water for oral administration, yet dissolve/disintegrate in mouth in a matter of seconds Leave minimal or no residue in mouth after administration. [2]

ADVANTAGES

- In this route of administration, the drug by passes the liver hence avoids drug metabolism, as well as the drug is protected from getting degraded by the gastric acids and digestive enzymes in the gastro intestinal tract
- Drug is absorbed more rapidly which will successfully provide rapid onset of action.
- It is easy to administer. No technical help is required, even to administer to those patients who are unable to swallow a tablet, e.g. pediatric, psychiatric patients and geriatric patients.
- The large contact surface of the oral cavity contributes to rapid and extensive drug absorption
- The dosage form is not to be swallowed hence there is no need of water for such drug administration
- It is better than liquid dosage forms.
- Some drugs are absorbed from the mouth pharynx and esophagus as the saliva passes down into the stomach, in such cases bioavailability of drugs is increased.
- It has improved bioavailability due to pregastric absorption hence dosage can be reducing; it has good clinical performance and has less unwanted effects.
- Good mouth feels property helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.
- Good patient compliance due to no associated pain with drug administration like in the case of injectables
- Better suitability in administration of drug and precise dosing. [3]

DISADVANTAGES

- Sublingual administration of drugs interferes with eating, drinking, and talking, so this route cannot be considered for prolonged administration.
- As the drug absorption is rapid, this site is not well suited to sustained-delivery systems.
- Not suitable for bitter drugs delivery can lead to poor patient compliance.
- 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.
- Administration of highly ionic drug and high dose of drug is impossible. [4]

1.2 MECHANISM INVOLVED IN SUBLINGUAL ABSORPTION

The sublingual mucosal lining consists of three distinct layers. ***The outermost layer is the epithelial membrane,*** which consists of stratified squamous epithelial cells and has a protective barrier function. ***The innermost layer of the epithelial membrane is called the basement membrane*** that replenishes the epithelium. Below the epithelium lies the ***lamina propria*** followed by the sub mucosa. The lamina propria is a hydrated and less dense layer of connective tissue containing collagen and elastic fibers. The oral Sub mucosa is also richly supplied with blood vessels. The following absorption through the mucous membrane in the sublingual region, the drug instantly gets absorbed into venous blood. The absorption potential of buccal mucosa is affected by the lipid solubility, the permeability of the solution

(osmosis), the ionization (pH), and the molecular weight of the substances. The venous blood from the sublingual region of the oral cavity drains into a common trunk, which then drains via the internal jugular vein, the subclavian vein, and the brachiocephalic vein directly into the superior vena cava. Thus, venous return from these regions enters the systemic circulation, bypassing the pre-systemic drug elimination, unlike in oral administration. Direct drainage into systemic circulation results in the immediate systemic availability of the drug and rapid onset of action. It should be noted that smoking, which causes vasoconstriction, may affect drug absorption. In sublingual glands, the patterns of different branches are compact. The venous blood from the sublingual region of the oral cavity drains into a common trunk, which then drains through the internal jugular vein, the subclavian vein, and the brachiocephalic vein directly into the superior vena cavaun like in oral administration. [5]

2. FACTORS AFFECTING THE SUBLINGUAL ABSORPTION

a. **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 the thinner epithelium and also the immersion of drug in smaller volume of saliva.

b. **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. [6]

c. **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.

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

e. **Solubility in salivary secretion**: In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e. biphasic solubility of the drug is necessary for absorption.

f. **Binding to oral mucosa**: Systemic availability of drugs that bind to oral mucosa is poor.

3. SUITABILITY OF DRUG FOR PREPARATION OF SUBLINGUAL DRUG DELIVERY

- The drug should not have bitter taste.
- Dose lowers than 20 mg, e.g. Nifedipine
- the drug Should be of small to moderate molecular weight
- The drug should have good stability in water and saliva.
- Remain partially non-ionized at the oral pH.
- Undergoing first pass effect.
- Many drug properties could potentially affect the performance of sublingual tablets like solubility, crystal morphology, particle size, hygroscopicity, compressibility and bulk density of drug.
- Some drugs undergoes extensive first pass metabolism which results in poor bioavailability of its oral dosage forms, that kind of drugs are suitable for sublingual dosage form.
- Drugs that are unstable in parenteral preparation are suitable for sublingual dosage form.
- Many pharmaceuticals are designed for sublingual administration, including cardiovascular drugs, steroids, barbiturates, enzymes, antiemetics, vitamins, minerals and vaccines Able to saturate the oral mucosa.
- Should have lower bio availability are good candidates for sublingual tablets
- Frequent dosing of drugs unsuitable for sublingual tablets
- Ability to permeate oral mucosa. [7]

4. SUBLINGUAL FORMULATIONS

- Sublingual Tablets
- Sublingual Films
- Multipurpose tablets
- Sublingual drops
- Sublingual spray
- Lozenge
- Effervescent sublingual tablets

4.1 METHOD OF PREPARATION OF SUBLINGUAL FORMULATIONS

4.2 Sublingual tablets

Various techniques can be used to formulate sublingual tablets.

4.2.1 Direct compression: It is one of the techniques which require the incorporation of a superdisintegrant into the formulation, or the use of highly water-soluble excipients to achieve fast tablet disintegration. Direct compression does not require the use of water or heat during the formulation

procedure and is the ideal method for moisture and heat-labile medications. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. 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 solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agent. Disintegration efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually required. As consequences, products with optimal disintegration properties often have medium to small size and/or high friability and low hardness. Several novel approaches of incorporating disintegrants and other soluble and/or insoluble excipients to obtain rapid dissolution and adequate mechanical strength are reported. One example is the Flashtab technology of multiparticulate actives (coated crystals and uncoated or coated microgranules). In these tablets, the simultaneous presence of a disintegrant with a high swelling or disintegrating force, defined as "disintegrating agent," and a substance with a low swelling force (starch, cellulose, and direct compression sugar), defined as "swelling agent," was claimed as the key factor for the rapid disintegration of a tablet. The tablet manufactured by this technology is reported to have adequate mechanical strength. [8]

Advantages

- Low labor input
- A dry process
- Fewest processing steps

Disadvantages

Stratification may occur due to differences in particle size and bulk density which results poor content uniformity. A large dose drug may cause problem in direct compression. It requires diluents. The tablet becomes large in size which is difficult to swallow and also costly. During handling of dry materials static charge may form which may present uniform distribution of drug. Direct compression diluents may interact with the drug. For example, amine drug with Lactose produces discoloration of tablet. [9]

4.2.2 Compression molding

Tablets produced by this method will disintegrate and dissolved rapidly (within 4 to 11 sec). Disadvantage of this method is tablets having poor mechanical strength, to overcome. These problem binders are added to formulation blend. Tablets manufactured by this method pose special challenges during handling or shipping and because of the poor mechanical strength or may require special packaging. However, the binder level should be optimized to avoid any deleterious effects on disintegration and dissolution of the tablets. The formulations for the compression molding process typically contain soluble excipients to impart quick and complete dissolution, and taste modifiers for patient compliance. Molded tablets have also been prepared directly from a molten matrix, in which the drug is dissolved or dispersed (heat molding), or by evaporating the solvent from a drug solution or suspension at room pressure (no vacuum lyophilization). The compression molding process involves moistening of the formulation blend with a solvent (usually hydro-alcoholic), followed by molding into tablets under low pressure. The moist tablets are finally dried. The lower compression pressure employed for molding and drying of the moist tablet produces a highly porous tablet structure with enhanced dissolution. The choice, ratio, and amount of granulating solvents are critical to the physicochemical characteristics, performance, and stability of the tablets, and should be optimized. Several patented technologies are also available for commercial manufacture of compression molded tablets. [10]

4.2.3 Freeze Drying (Lyophilization):

The process of freeze drying (lyophilization) is expensive, time consuming, and produces tablets of poor mechanical strength. For these reasons, it is not commonly used to manufacture sublingual tablets. However, it does have advantages over the other processes, as the tablets made by this process have high porosity, and when placed under the tongue disintegrate and dissolve immediately. It is a process of choice for products that are unstable or are heat sensitive. The process involves lowering the temperature of the product in an aqueous medium to below freezing, followed by applying a high-pressure vacuum. To extract the water in the form of a vapor, which is collected as ice on a condenser, a gradual temperature rise is applied during the drying process. The product temperature at the ice sublimation interface and the formulation collapse temperature are critical to obtain a freeze-dried cake of quality structure. This process retains the physical structure and preserves the material for storage or transport. The resulting tablets are usually light and have highly porous structures that allow rapid dissolution or disintegration. The freeze-drying process may result in a product with an amorphous structure, leading to an enhanced dissolution rate. However, tablets manufactured by freeze drying process have poor stability at a higher temperature and humidity. [11]

4.2.4 Spray Drying:
In spray drying process, highly porous and fine powder can be produced and processing solvent is evaporated during process. Spray dryers are widely used in pharmaceuticals and biochemical process. Spray drying can be used to prepare rapidly disintegrating tablets by using support matrix such as hydrolyzed and non-hydrolyzed gelatin and other components like Mannitol as bulking agent, sodium starch glycolate, and Crosscarmellose sodium as disintegrants, acidic material like citric acid and alkali like sodium bicarbonate to enhance disintegration and dissolution. The tablet manufactured from this process, disintegrated in less than 20 seconds in an aqueous medium. [12]

4.2.5 Sublimation:
The key to rapid disintegration for mouth dissolving tablet is the presence of a porous structure in the tablet matrix. Conventional compressed tablet that contains highly water-soluble ingredients often fail to dissolve rapidly because of low porosity of the matrix. Hence, to generate porous matrix, volatile ingredients are used that are later subjected to a process of sublimation. The volatile material was then removed by sublimation and that result in formation of a porous matrix (approximately 30%). Other methods like mass extrusion and disintegrate addition can also be used. [12]

4.2.6 Evaluation
- Surface pH of the tablet
- Uniformity of weight
- Content uniformity
- Hardness
- Thickness
- Diameter
- Disintegration time
- Wetting time and
- Friability

4.2.7 SUPERDISINTEGRANTS:
Disintegrating agents are substances routinely included in the tablet formulations to aid in the break-up of the compacted mass into the primary particles to facilitate the dissolution or release of the active ingredients when it is put into a fluid environment. They endorse moisture penetration and dispersion of the tablet matrix. The major function of disintegrants is to oppose the efficiency of the tablet binder and physical forces that act under compression to structure the tablet. Recently new materials termed as “superdisintegrants” have been developed to improve the disintegration processes. Superdisintegrants are another version of super-absorbing materials with tailor-made swelling properties. These materials are not planned to absorb significant amounts of water or aqueous fluids, but planned to swell very fast. Superdisintegrants are used as a structural weakener for the disintegrable solid dosage forms. They are physically dispersed within the matrix of the dosage form and will expand when the dosage form is exposed to the wet environment. These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1 - 10 % by weight relative to the total weight of the dosage unit. Their particles are generally small and porous, which allow for rapid tablet disintegration in the mouth without an objectionable mouth-feel from either large particles or gelling. The particles are also compressible which improves tablet hardness and its friability. Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs. Generally, one gram of superdisintegrant absorbs 10-40 g of water or aqueous medium. After absorption, swelling pressure and isotropic swelling of the superdisintegrants particles create stress concentrated areas where a gradient of mechanical properties will exist due to which whole structure will break apart. [13]

4.2.8 Mechanism of Superdisintegrants
Superdisintegrants are used to improve the efficacy of solid dosage forms. This is achieved by various mechanisms. The mechanism by which the tablets are broken into small pieces and then produces a homogeneous suspension is based on:

- Swelling
- Porosity and capillary action (Wicking)
- Heat of wetting
- Chemical reaction (Acid-Base reaction)
- Particle repulsive forces
- Deformation recovery
- Enzymatic reaction

4.2.9 Swelling:
Although water penetration is a necessary first step for disintegration, swelling is probably the most widely accepted mechanism of action for tablet disintegrants. Particles of disintegrants swell on coming in contact with suitable medium and a swelling force develops which leads to break-up of the matrix. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to

note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down. [14]

4.2.10 Porosity and capillary action (Wicking)
Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablet porosity provides pathways for the penetration of fluid into tablets. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles. [14]

4.2.11 Heat of wetting:
When disintegrants with exothermic properties get wetted, localized stress is created due to capillary air expansion, which aids in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

4.2.12 Chemical reaction (Acid-Base reaction):
The tablet is quickly broken apart by internal liberation of CO_2 in water due to interaction between tartaric acid and citric acid (acids) with alkali metal carbonates or bicarbonates (bases) in presence of water. The tablet disintegrates due to generation of pressure within the tablet. Due to liberation in CO_2 gas, the dissolution of active pharmaceutical ingredients in water as well as taste masking effect is enhanced. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during preparation of the tablets. The effervescent blend is either added immediately prior to compression or can be added in two separate fraction of formulation. [15]

4.2.13 Particle Repulsive Forces:
This is another mechanism of disintegration that attempts to explain the swelling of tablet made with non-swellable disintegrants. According to Guyot-Hermann's particle-particle repulsion theory, water penetrates into tablet through hydrophilic pores and a continuous starch network is created that can convey water from one particle to the next, imparting a significant hydrostatic pressure. The water then penetrates between starch grains because of its affinity for starch surfaces, thereby breaking hydrogen bonds and other forces holding the tablet together. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. [15]

4.2.14 Deformation Recovery:
Deformation recovery theory implies that the shape of disintegrant particles is distorted during compression and the particles return to their pre-compression shape upon wetting, thereby this increase in size of the deformed particles causing the tablet to break apart. Such a phenomenon may be an important aspect of the mechanism of action of disintegrants such as Crospovidone and starch that exhibit little or no swelling.

4.2.15 By Enzymatic Reaction:

Enzymes present in the body also act as disintegrants. These enzymes dearth the binding action of binder and helps in disintegration. Due to swelling, pressure is exerted in the outer direction that causes the tablet to burst or the accelerated absorption of water leads to an enormous increase in the volume of granules to promote disintegration. [16]

4.2.16 SYNTHETIC SUPERDISINTEGRANTS:

Synthetic super- disintegrants are frequently used in tablet formulations to improve the rate and extent of tablet disintegration thereby increasing the rate of drug dissolution. The most widely used synthetic superdisintegrants are illustrated below.

4.2.17 Cross-linked polyvinyl Pyrrolidone (Crospovidone):
Unlike other superdisintegrants, which rely principally on swelling for disintegration, crospovidone use a combination of swelling and wicking. Due to its high crosslink density, crospovidone swells rapidly in water without gelling. Crospovidone particles are found to be granular and highly porous which facilitates wicking of liquid into the tablet and particles to generate rapid disintegration. Larger particles provide a faster disintegration than smaller particles. Crospovidone disintegrants are highly compressible materials as a result of their unique particle morphology. Crospovidone can also be used as solubility enhancer. It is available in two particle sizes in the form of Polyplasdone XL and Polyplasdone XL-10. [16]

4.2.1 8 Croscarmellose Sodium:

It is an internally cross-linked polymer of carboxymethyl cellulose sodium. It has high swelling capacity with minimal gelling resulting in rapid disintegration. Due to fibrous structure, croscarmellose particles also show wicking action. In tablet formulations, croscarmellose sodium may be used in both direct compression and wet-granulation processes. When used in wet-granulation, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extra-granularly) so that the wicking and swelling ability of the disintegrant is best utilized.

4.2.19 Sodium Starch Glycolate:

Sodium Starch Glycolate is the sodium salt of a carboxy methyl ether of starch. These are modified starches made by cross linking of potato starch as it gives the product with the best disintegrating properties. The degree of cross-linking and substitution are important factors in determining the effectiveness of these materials as super disintegrants. The effect of the cross linking is to reduce both the water-soluble fraction of the polymer and the viscosity of dispersion in water. The natural pre dried starches swell in water to the extent of 10-20 percent and the modified starches increase in volume by 200-300 percent in water. The mechanism by which this action takes place involves rapid absorption of water leading to an enormous increase in volume of granules that result in rapid and uniform disintegration. These are available as explotab and primogel which are low substituted carboxy methyl starches. The effect of introduction of the large hydrophilic carboxymethyl groups is to disrupt the hydrogen bonding within the polymer structure. This allows water to penetrate the molecule and the polymer becomes cold water soluble. [16]

Advantages of Synthetic Super disintegrants:

- Effective in lower concentrations than starch.
- Less effect on compressibility and flow ability.
- More effective intragranularly.

However, there are a number of limitations that superdisintegrants practically impose in pharmaceutical applications. For example

- More hygroscopic (may be a problem with moisture sensitive drugs)
- Some are anionic and may cause some slight *in-vitro* binding with cationic drugs (not a problem *in-vivo*).
- An acidic medium significantly reduces the liquid uptake rate and capacity of sodium starch glycolate and croscarmellose sodium, but not crospovidone .
- The degree of swelling of Primojel1 (sodium starch glycolate) and Polyplasdone XL101 (crospovidone) is minimized following wet granulation formulation. Finally, the medium ionic strength was found to have an adverse effect on the swelling capacity of croscarmellose. [16]

Therefore, natural superdisintegrants serve as a better alternative to overcome the shortcomings of these superdisintegrants .

4.2.21 NATURAL SUPERDISINTEGRANT:

Today, we have a number of plant-based pharmaceutical excipients and various researchers have explored the utility of some of these plant-based materials as pharmaceutical superdisintegrants. Plant products serve as an alternative to synthetic products because of local accessibility, eco-friendly nature, bio-acceptable, renewable source and lower prices compared to important synthetic products. Majority of investigations on natural polymers for disintegrant activity are centered on polysaccharides and proteins, due to their ability to produce a wide range of materials and properties based on their molecular structures. Polysaccharide hydrocolloids including mucilages, gums and glucans are abundant in nature and generally found in many higher plants. Mucilages are merely secondary plant metabolites, but due to the high concentration of hydroxyl groups in the polysaccharide, mucilages generally have a high water-binding capacity and this has led to studies of their role in plant water relations. It has been suggested that the ability of mucilage to hydrate may offer a mechanism for plants to resist drought. Therefore, natural gums and mucilages have been widely explored as disintegrants. Mucilages and gums are well known since ancient times for their medicinal use. In modern era they are widely used in pharmaceutical industries as thickeners, water retention agents, suspending agents and superdisintegrants. Mucilage is glutinous substance which mainly consists of polysaccharides, proteins and uranides. Dried up mucilage or the concentrated mucilage is called as Gum. The main difference between them is that mucilage does not dissolve in water whereas gum dissolves in water. Mucilage is formed in the normal growth of plant by mucilage

secreting glands. Naturally the demand of these substances is increasing and new sources are tapped. India due to geographical and environmental positioning has traditionally been a good source for such products. [17]

4.2.22 Hibiscus rosa-sinensis Linn. Mucilage:

Hibiscus rosa-sinensis Linn of the *Malvaceae* family is also known as the shoe-flower plant, China rose, and Chinese hibiscus. The plant is available in India in large quantities and its mucilage has been found to act as a superdisintegrant. The plant contains cyclopropanoids, methyl sterculate, methyl-2-hydroxysterculate, 2-hydroxysterculate malvate and β-rosasterol. The leaves contain carotene (7.34 mg/100 g of fresh material) moisture, protein, fat, carbohydrate, fibers, calcium, and phosphorus. Mucilage of *Hibiscus rosa-sinensis* contains L-rhamnose, D-galactose, D-galactouronic acid, and D-glucuronic acid. The percentage yield of mucilage is estimated as 17%. Other physicochemical parameters of mucilage are also evaluated. The results of swelling ratio, angle of repose, bulk density and compressibility index are observed as 9, 26.5ºC, 0.65g/cc, 16% respectively.

4.2.23 Isapghula Husk Mucilage (*Plantago ovata*):

Isapghula Husk consists of dried seeds of the plant known as plantago ovata. The plant contains mucilage in the epidermis of the seeds. Mucilage of plantago ovata has various characteristics like binding, disintegrating and sustaining properties. Mucilage can be used as superdisintegrant to formulate fast dissolving tablets because it has very high percentage of swelling index (around 89±2.2%v/v) as compared to the other superdisintegrating agents. The rapid disintegration of the FDTs is due to the swelling of superdisintegrants to create enough hydrodynamic pressure for quick and complete disintegration of the tablet. The rate at which swelling develops and significant force of swelling also determine its disintegrating efficiency.

4.2.24 Cucurbita maxima pulp powder:

Cucurbita maxima fruit was cleaned with water to remove dust from surface and further peel was removed. The seed was removed and pulp was put into juicer mixer to form highly viscous liquid. This was further lyophilized to get solid porous mass. Size reduction was done and powder was collected. The collected powder was passed through 80 # sieve and stored for further study. Study revealed that *Cucurbita maxima* pulp powder have comparable dissolution behavior to that of sodium starch glycolate. It also has comparable hardness and friability thus the naturally obtained *Cucurbita maxima* pulp powder stands as a good candidate to act as disintegrant and it is possible to design promising Fast disintegrating tablet using this polymer. [17]

4.2.25 Lepidium sativum Seed Mucilage:

Natural *Lepidium sativum* (family: Cruciferae), also known as asaliyo, has wide application in pharmaceutical field as disintegrating agent and as herbal medicine. Seeds contain a higher proportion of mucilage, dimeric imidazole alkaloids lepidine B, C, D, E and F and two new monomeric imidazole alkaloids semilepidinoside A and B. The mucilage can be extracted from seeds by different procedures and its yield varies from 14% to 22%. Mucilage of *Lepidium sativum* has various characteristic like binding, disintegrating, gelling etc. The extracted mucilage is used to develop fast dissolving tablets. Mucilage is found to be a brownish white powder which decomposes above 200ºC and have characteristic odour. On evaluating its various physicochemical characteristics, the values of swelling index, angle of repose, bulk density and tapped density are estimated as following 18, 32ºC, 0.58g/cc and 0.69g/cc respectively.

4.2.26 Fenugreek Seed Mucilage:

Trigonella Foenum-graceum (family Leguminosae), commonly known as Fenugreek, is an herbaceous plant of the leguminous family. It is one of the oldest cultivated plants and has found wide applications as a food, a food additive, and as a traditional medicine in every region. Fenugreek seeds contain a high percentage of mucilage which can be used as disintegrant for use in mouth dissolving tablet formulations. Mucilage is an off white-cream yellow colored amorphous powder that quickly dissolves in warm water to form viscous colloidal solution. Its physicochemical parameters are studied and found to have 22.25ºC, 0.64g/cc, 15.20% values as angle of repose, bulk density and compressibility index respectively. [17]

4.2.27 Chitosan:

Chitosan is a natural polymer obtained by deacetylation of chitin which is the second most abundant polysaccharides in nature after cellulose. Superdisintegrant property of chitosan has been utilized to develop a fast mouth dissolving tablet by utilizing a novel method. Similar to the other superdisintegrants chitosan too generously engulf water when in contact with aqueous media and burst due to the pressure exerted by their capillary action thereby impart instantaneous disintegration of the

dosage form and resulting in formation of a uniform dispersion in the surrounding media which behave like a true suspension formed inside the body leading to rapid and complete absorption of drug. Mucilage of natural origin is preferred over semi-synthetic and synthetic substances because they are comparatively cheaper, abundantly available, non-irritating and nontoxic in nature.

4.2.28 Gums:

Gums have been used as disintegrants because of their tendency to swell in water. They can perform good disintegration characteristics (2-10%)

4.3 **FILMS**

Thin film drug delivery is a process of delivering drugs to the systemic circulation via a thin film that dissolves when in contact with liquid, often referred to as a dissolving film or strip. Thin film strips are typically designed for oral administration, with the user placing the strip on or under the tongue or along the inside of the cheek. As the strip dissolves, the drug can enter the blood stream enterically, buccally or sublingually. The sublingual delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing, and enhance the efficacy and safety profile of the medicament. All tablet dosage forms, softgels and liquid formulations primarily enter the blood stream via the gastrointestinal tract, which subjects the drug to degradation from stomach acid, bile, digestive enzymes and other first pass effects. As a result, such formulations often require higher doses and generally have a delayed onset of action. Conversely, sublingual thin film drug delivery can avoid these issues and yield quicker onsets of action at lower doses. Thin film is more stable, durable and quicker dissolving than other conventional dosage forms. Thin film enables improved dosing accuracy relative to liquid formulations since every strip is manufactured to contain a precise amount of the drug. Thin film not only ensures more accurate administration of drugs but also can improve compliance due to the intuitive nature of the dosage form and its inherent ease of administration. These properties are especially beneficial for pediatric, geriatric and neurodegenerative disease patients where proper and complete dosing can be difficult. Thin film's ability to dissolve rapidly without the need for water provides an alternative to patients with swallowing disorders and to patients suffering from nausea, such as those patients receiving chemotherapy. Thin film drug delivery has the potential to allow the development of sensitive drug targets that may otherwise not be possible in tablet or liquid formulations. From a commercial perspective thin film drug delivery technology offers an opportunity to extend revenue lifecycles for pharmaceutical companies whose drug patent is expiring and will soon be vulnerable to generic competition. 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. 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 minutes when compared with immediate release oral tablets (1.3 hours), intramuscular (1 hour),and intranasal oxycodone (0.42 hour) in healthy volunteers. [18]

4.3.1 Evaluation

- Uniformity of content
- Uniformity of weight
- Uniformity of thickness
- Surface pH
- Folding endurance
- % Flatness
- % Elongation
- Tensile strength
- Module of elasticity
- In-vitro dissolution diffusion
-

4.4 Sublingual Drops

Concentrated solutions to be dropped under the tongue, as with some nicocodeine cough preparatations.

4.5 Sublingual Spray

Spray for the tongue; certain human and veterinary drugs are dispensed as such.

4.6 Lozenge

Effects a metred and patient-controlled-rate combination of sublingual, buccal, and oral administration, as with the Actiq fentanyl lozenge-on-a-stick (lollipop).

4.7 Effervescent Sublingual Tablets

This method drives the drug through the mucous membranes much faster (this is the case in the stomach with carbonated or effervescent liquids as well) and is used in the Fentora fentanyl tablet.

5. EVALUATION TESTS FOR TABLETS

5.1 Physical Evaluation

All batches of sublingual formulations like tablets and films were evaluated for weight variation and drug content. But hardness and friability were calculated for tablets. As the hardness of sublingual tablet is an important factor because if the sublingual tablet is too hard, the solvent-borne drug attenuation may not occur into the interior portion of the tablet and therefore remain on a surface portion of the tablet, where the drug attenuation may not adhere to the sublingual tablet. If the sublingual tablet is too soft, the sublingual tablet may be disintegrated by the solvent of the drug attenuation. Preferably, the solvent-borne drug attenuation should be absorbed into the interior of the sublingual tablet. Weight variation test is conducted by selecting 20 tablets at random as per I. P. Sublingual films were also evaluated for thickness using micrometer screw gauge , tensile strength , folding endurance , surface pH , and swelling index. [19]

5.2 Drug-Polymer Interaction Study of film:

There is always a possibility of drug-excipient interaction in any formulation due to their intimate contact. The technique employed in this study to know drug-excipient interactions is IR spectroscopy; IR spectroscopy is one of the most powerful analytical techniques which offer the possibility of chemical identification. Infra-red spectra of pure drug Drugand formulations were scanned by using Perkin-Elmer FTIR SV-10, by a thin film method.

5.3 Hardness test

The crushing strength (Kg/cm2) of prepared tablets was determined by using Monsanto hardness tester or Electro lab hardness tester. The hardness tests was performed for each batches of prepared tablets in triplicate manner. The tablets should be resistance to breakage under storage conditions.

5.4 *In vitro* dispersion time

This test can be done by taking 50 ml of Phosphate buffer pH 6.8, three tablets were tested from each batch and note the dispersion time.

5.5 Wetting time

A piece of tissue paper folded twice is placed in a small Petri dish Containing 6 ml of water. A tablet is put on the tissue paper and allowed to completely wet. The wetted tablet is then weighted. Water absorption ratio, R was determined using following equation.

$$R = 100 \times Wa - Wb/Wa$$

Where, Wa = Weight of tablet after water absorption, Wb = Weight of tablet before water absorption.

5.6 Friability

Roche friabilator can be utilized to decide the friability. Check the weight of tablets and place them in friabilator, The tablets were pivoted in the friabilator for no less than 4 minutes. At the end of test tablets were cleaned and reweighed, the misfortune in the heaviness of tablet is the measure of friability. Friability is calculated in percentage using following equation

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

or

$$\% \text{ Friability} = W_0 - W / W_0 \times 100$$

5.7 *In vitro* disintegration test

The test was carried out on 6 tablets using the apparatus specified in I.P.1996 distilled water at 37ºC±2ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds. This test can be performed by using USP disintegration apparatus, distilled water was used as medium. The time required to obtain complete disintegration of all tablets was noted.

5.8 *In vitro* dissolution test

Dissolution study was carried out in USP paddle type apparatus using 300 mL of stimulated salivary fluid (pH 6.8) as a dissolution medium at50rpm. Temperature of the dissolution medium was maintained at 37±0.5ºC. Samples of 5ml were withdrawn at every 4 minutes interval, filtered (through0.45µ) and replaced with 5ml of fresh dissolution medium. The samples were suitably diluted and estimated spectrophotometrically at specified nm by using double beam UV-Visible spectrophotometer. The dissolution experiments were conducted in triplicate. Dissolution rate was studied for all designed formulations and dissolution parameters were calculated. [20]

5.9 Drug Content

Randomly ten tablets are selected from formulation, finely powdered and powder equivalent mg of drug is accurately weighed and transferred to100ml volumetric flasks containing solution of desired pH. The flask is shaken to mix the contents thoroughly. The volume is made up to the mark with solution and filtered. One ml of the filtrate is suitably diluted and drug content is estimated using a double beam UV-visible spectrophotometer. This procedure is repeated thrice and the average value is calculated.

6. Evaluation Tests for Films

6.1 Weight Uniformity of film:

Weight variation is studied by individually weighing 3 randomly selected films and by calculating the

average weight. Thickness of films: The thickness of film is determined by micrometer screw gauge at 5 different points of the film i.e central and the four corners and means thickness is calculated. For measurement of Uniformity of thickness, 5 film are randomly selected and thickness is measured on location of each formulation Maximum variation in the thickness of the films should be less than 5% and mean ±S. D. is calculated.

6.2 Folding Endurance of film

Folding endurance is measured by manually repeated folding of film at same place till it broke. The number of times the film is folded without breaking is known as the folding endurance value. The flexibility or elasticity of film can be measured. Folding endurance was measured by manually or practically for the prepared films. Take a 2X2cm films and folded repeatedly at the same place till it broke. The no times the film could be folded at the same place without breaking gave the exact valve of folding endurance. [21]

6.3 Surface pH of film

The film to be tested was placed in a Petridis and was moistened with 1ml of distilled water and kept for 30s. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1min. The average of three determinations for each formulation was done. [22]

6.4 Drug content uniformity of films:

Standard solution:

Accurately about 10mg of drug was weighted and transferred in to a 10 ml of volumetric flask. Then add PBS (pH 6.8) solution with mechanical shaking up to 10 ml (1000 µg/ml). Then this solution was filtered through the whatman filter paper. Then 0.1 ml of filtrate was pipette out and diluted up to 10 ml with the PBS solution in 10 ml of volumetric flask so as to get 10 µg/ml final concentrations.

Test solution:

One film of was dropped into a 10 ml of volumetric flask. Then add PBS (pH 6.8) solution with mechanical shaking up to 10 ml. Then this solution was filtered through the whatman filter paper. Then 0.1 ml of filtrate was pipette out and diluted up to 10 ml with the PBS solution in 10 ml of volumetric flask so as to get 10 µg/ml final concentration. Content uniformity was calculated using following formula:

%Label claim = Abt /Abs x Ds/ Dt x 100 /Lc x100.

Where, Abs = Abs. of standard solution, Lc = Label claim, Ds = Dilution of standard, Dt = Dilution of test, Abt = Abs. of test solution. [23]

6.5 *In vitro* Drug Release:

The release rate of the fast-dissolving film was determined by the help of USP Dissolution Test Apparatus-II. The dissolution test was performed using 300 ml Phosphate Buffer Solution pH 6.8, at 37 ±0.50C with 50 rpm of the paddle speed. Aliquot 5 ml of the solution was collected from the dissolution apparatus at time interval of 1 min and at the same time add 5 ml or same amount of fresh dissolution medium. The Aliquot filtered through the whatman filter paper. The absorbance of the filtered solution was measured at prescribed nm. The aliquot should be withdrawn at the zone between the surface of the dissolution medium and the top of rotating paddle not less than 1 cm apart from the vessel wall. Cumulative percent drug release can be calculated by using the equation obtained from the standard curve or % drug release formula. [24]

(A = Con. of Std. / Abs. of Std. X Abs. of sample X volume of dissolution apparatus X Dilution factor / 1000,

B = AValue/Label claim X 100).

7. RECENT DEVELOPMENTS

Nitroglycerine-delivering sublingual aerosol formulation (nitro- glycerine in propellants) in a metered-dose spraying pump, Nitrolingual spray, was developed. It delivers nitroglycerine by spraying onto or under the tongue in the form of spray droplets, which ultimately increase the absorption and hence the bioavailability of nitroglycerine. The rapid onset of action is always required in case of hypertension. [25]

8. DRUGS USED IN SUBLINGUAL TABLETS. [26]

	Drug	Category	Dosage form
1.	Captopril	Antihypertensive agent	Tablet
2.	Furesamide	Diuretic	Tablet
3.	Scopolamine	Opioid analgesic	Spray
4.	Ondansatron Hcl	Antiemetic agent	Film
5.	Salbutamol Sulphate	Antiasthmatic agent	Film

9. MARKET PREPARATION [27]

- Tenormin sublingual tablet (isoproterenol)
- Microtab sublingual tablet (nicotine)
- Nascobal sublingual tablet (vitamin B12)
- Subuter sublingual tablet (buprenorphine)
- Nitroquick sublingual tablet (nitroglycerin)

10.CONCLUSION:

Sublingual drug delivery has been used for formulation of many drugs with view point of rapid drug release and quick onset of action. This review demonstrates that there are a number of commercially available sublingual formulations manufactured using various technologies. Many drugs have been formulated for sublingual drug delivery with an objective of rapid drug release and restricting the region of drug release to mouth. Compared to commonly used tablets, capsules and other oral dosage forms, sublingual absorption is generally much faster and more efficient. Sublingual dosages are convenient for young children, the elderly and patients with swallowing difficulties, and in situations where potable liquids are not available. [28] Peak blood levels of most products administered sublingually are achievedwithin10-15 minutes, which is generally much faster than when those same drugs are ingested orally. Sublingual absorption is efficient. The percent of each dose absorbed is generally higher than that achieved by means of oral ingestion. The publically available information on sublingual tablets implies that this dosage form has good potential to enhance drug delivery in treating a number of indications. Various types of sublingual dosage forms are available in market like tablets, films, sprays, Drops, Lozenge etc. In most reported cases, it has been shown that the sublingual dosage form not only improves the patient's compliance, but also reduces the time for the onset of the drug action, and increases the bioavailability of drugs as compared to conventional tablets. Therefore, sublingual tablets are an accepted technology for systemic delivery of drugs. [29]

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