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REVIEW ARTICLE

SUBLINGUAL TABLETS: AN OVERVIEW

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ABSTRACT

Drug delivery via the oral mucous membrane is considered to be a promising alternative to the oral route. Sublingual route is a useful when rapid onset of action is desired with better patient compliance than orally ingested tablets. In terms of permeability, the sublingual area of the oral cavity (i.e. the floor of the mouth) is more permeable than the buccal (cheek) area, which in turn is more permeable than the palatal (roof of the mouth) area. The portion of drug absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes giving acceptable bioavailability. Sublingual technology for patients need enhanced lifecycle management to convenient dosing for geriatric, pediatric and patient with dysphagia. This review highlights the sublingual dosage forms for the treatment of migraine, factors affecting the sublingual absorption, advantages, various *in vitro* and *in vivo* evaluation parameters and commercially available sublingual dosage forms.

Keywords: Improved bioavailability, Sublingual delivery, Dysphagia, Technique.

INTRODUCTION

Oral administration is a route of administration where a substance is taken through the mouth. Many medications are taken orally because they are intended to have a systemic effect, reaching different parts of the body via the bloodstream.

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablet. [(1)]

Solid medicaments may be administered orally as powders, pills, cachets, capsules or tablets. These dosage forms contain a quantity of drug which is given as a single unit and they are known collectively as solid unit dosage forms, even in the case of sustained action preparations which, technically, contain the equivalent of several normal doses of drug.[(2)]

Tablet that disintegrates or dissolve rapidly in the patients mouth are convenient for young children, elderly patients, mentally retarded and bedridden patients who used to suffer most probably with the problem of dysphagia and hand tremors. A fast dissolving sublingual tablet when placed in the mouth, rapidly get dispersed or dissolved and swallowed in the form of liquid. When sublingual tablets placed under the tongue, it produces immediate systemic effect by enabling the drug absorbed quickly or directly through mucosal lining of the mouth beneath

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the tongue. The drug absorbed from stomach goes to mesenteric circulation which connects through portal vein. Thus absorption through oral cavity avoid first pass metabolism. The sublingual tablets are usually small and flat, compressed lightly to keep them soft. The tablets must dissolve quickly allowing the API to be absorbed quickly. Its designed to dissolve in small quantity of saliva; after the tablet is placed in the mouth below the tongue, the patient should avoid eating, drinking, smoking and possibly talking in order to keep the tablet in place. Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological action.(3) Sublingual products have been designed for numerous indications ranging from migraine (for which rapid onset of action is important) to mental illness(for which patient compliance is important for treating chronic indications such as depression and schizophrenia) . Sublingual route provides [3-10] times greater absorption of the drug than oral route and is only surpassed by hypodermic injection. Sublingual route is very much appropriate for short-acting drugs. Most of the drugs which are administered through the sublingual route are absorbed by simple diffusion; here the sublingual area acts like a litmus paper readily soaking up the substances; however not all the substances are permeable and accessible to oral mucosa. Majority of drugs which are administered through sublingual route falls in the category of antianginal drug. Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological effect. Sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first pass metabolic processes.(4) Because of underdeveloped muscular and nervous system swallowing problems is common in childrens, and this could be easily overcome with the help of fast disintegrating sublingual tablets. Oral route of drug administration has been considered as the most popular one because it holds an edge over other routes such as it is the most natural , uncomplicated, convenient, safe means to administer drugs, greater flexibility in dosage form design , ease of production and low cost. By selecting the appropriate pharmaceutical excipients in the correct proportion, in combination with optimal manufacturing techniques the sublingual tablets could be prepared effectively. (5)

DIFFERENT TYPES OF TABLETS

Compressed tablets are prepared by single compression using tablet ma-chines. After a quantity of powdered or granulated tableting material flow into a die, the upper and lower punches of the tablet machine compress the material under a high pressure (~tons/in2).

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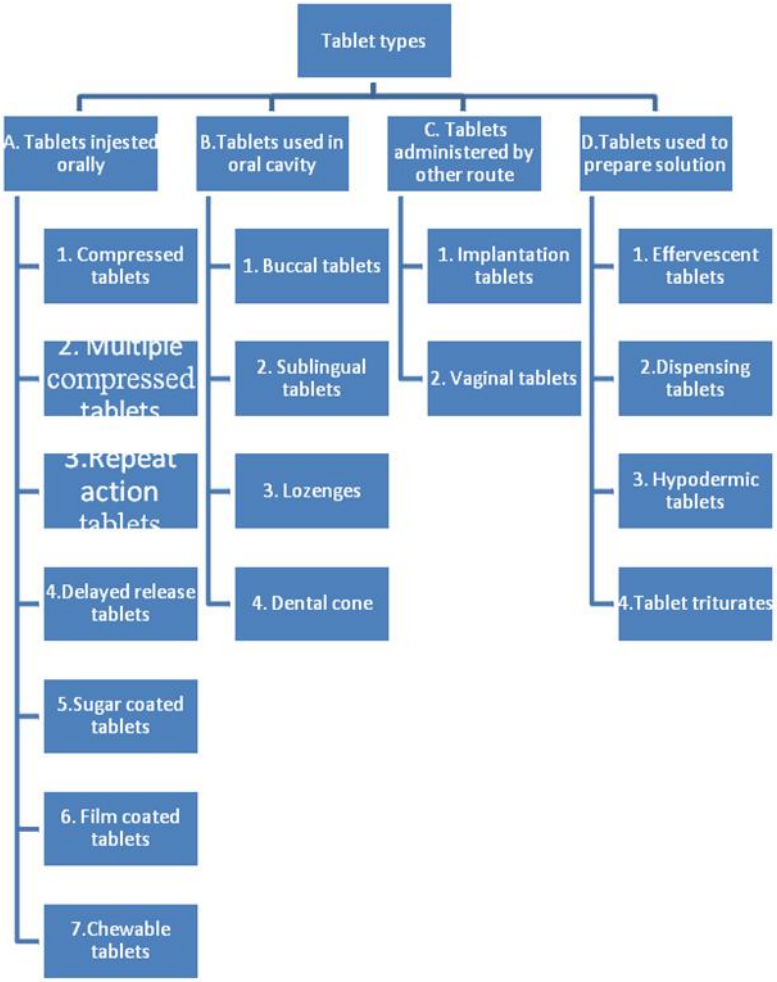

Figure 1 : Different types of tablets[6]

A. Tablets ingested orally

1. Compressed tablets: Standard uncoated tablets are manufactured by compression. The general methods are by wet granulation, dry granulation or direct compression, used for rapid disintegration and drug release. Both type of action – systemic effect and local effect.

2. Multiple compressed tablets: For incompatible components these are:

A) Layered tablet- either two layered (for two components) or three layered (for three components) tablet.

B) Compressed coated type- either tablet within a tablet or tablet within a tablet within a tablet. Tablet in this category are usually prepared for two reasons

1. To separate physically or chemically incompatible ingredients.
2. To produce repeat action or prolong action product. [7]

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3. Repeat action tablet: Sugar coated or multiple compressed tablets are used for this purpose .The core tablet is usually coated with shellac or an enteric polymer so that it will not release its drug in stomach but intestine.

4. Delayed action and enteric-coated tablet: This dosage form is intended to release the drug after some time delay or after the tablet has passed one part of the gastrointestinal tract into another. All enteric coated tablets are type of delayed action tablet but all delayed action tablets are not enteric or not intended to produce enteric action.

5. Sugar coated tablet: Primary role is to produce an elegant, glossy, easy to swallow, widely utilized in preparing multivitamin and multivitamin mineral combination. Sugar coating doubled the tablet weight. Now polymers are used with sugar solution.

6. Film coated tablet: One type of coated tablet in which drug is not required in coating. This is an attractive method within one or two hours. Polymers such as hydroxypropylcellulose, hydroxypropylmethyl cellulose, and colloidal dispersion of ethyl cellulose are commonly used. A 30% dispersion of ethyl cellulose is known as aquacoat. Advantage of film coated over sugar coated tablets is better mechanical strength and flexibility of the coating, little increase in tablet weight.

7. Chewable tablet: These are intended to be chewed in the mouth before swallowing. Used for large tablet of antacid, bitter or foul testing drugs are not suitable for this type tablet. [8]

B. Tablets used in oral cavity

1. Buccal and sublingual tablet: These tablets are small, flat and are intended to be held between the cheek and teeth or in cheek pouch (buccal tablet) or below the tongue (sublingual tablet). Drugs used by this route are for quick systematic action. The tablets are designed not to be disintegrate but slowly dissolve.

2. Troches and lozenges: Used in the oral cavity to exert local effect in mouth and throat. They are commonly used to treat sore throat or to control coughing in common cold. They may contain local anesthetics, antiseptic, antibacterial agents, demulcents, astringent and antitussive. The tablets are dissolving slowly over a period of 30 minutes.

3. Dental cone: These tablets are designed to be placed in the empty socket remaining after tooth extraction. Main purpose is to prevent microbial growth in the socket or to reduce bleeding. [9]

C. Tablets used by other route

1. Implantation tablets: designed for substances implantation to provide prolonged drug effect from one month to a year, tablets are usually small, cylindrical not more than 8mm length. These methods require special surgical technique for implantation and discontinuation of therapy. Generally used for administration of growth hormone to food producing animal.

2. Vaginal tablets: These are designed to undergo slow dissolution and drug release in vaginal cavity. Tablets are wide or pear shaped, used to antibacterial, antiseptic and astringent to treat vaginal infection. [10]

D. Tablets used to prepare solution

1. Effervescent tablets: Tablets are designed to produce a solution rapidly with the release of carbon dioxide. The tablets are prepared by compressing the active ingredient with mixture of organic acid such as citric acid or tartaric acid and sodium bicarbonate.

2. Dispersing tablets: Tablets are intended to be added to a given volume of water to produce a solution of a given drug concentration.

3. Hypodermic tablets: These tablets are composed of one or more drugs with water-soluble ingredients. Drug is added to sterile water to prepare sterile solution, which is injectable.

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4. Tablet triturates: Usually are made from moist materials using a triturate mold, which gives them the shape of cylinder. Such tablet must be completely and rapidly soluble. [11]

SUBLINGUAL TABLETS

They are to be placed under the tongue and produce immediate systemic effect by enabling the drug absorbed directly through mucosal lining of the mouth beneath the tongue. The drug absorbed from stomach goes to mesenteric circulation which connects to stomach via portal vein. Thus absorption through oral cavity avoids first pass metabolism. The tablets are usually small and flat, compressed lightly to keep them soft. The tablet must dissolve quickly allowing the drugs to be absorbed quickly. Table 1 depicts the drugs which have been used in formulation of sublingual tablets. [12] It is designed to dissolve in small quantity of saliva. After the tablet is placed in the mouth below the tongue, the patient should avoid eating, drinking, smoking and possibly talking in order to keep the tablet in place. Swallowing of saliva should also be avoided since the saliva may contain dissolved drug. Bland excipients are used to avoid salivary stimulation. Table 2 depicts the excipients used in formulation of sublingual tablets. Various techniques can be used to formulate rapidly disintegrating or dissolving tablets. [13]

Direct compression is one of these techniques which require 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. [14]

Sublingual, meaning literally 'under the tongue' refers to a method of administering substances via the mouth in such a way that the substances are rapidly absorbed via the blood vessels under the tongue rather than via the digestive tract. There is considerable evidence that most sublingual substances are absorbed by simple diffusion; the sublingual area acting rather likes litmus paper, readily soaking up the substances. However, not all substances are permeable and accessible to oral mucosa.

Advantages

- Ease of administration to patients who refuse to swallow a tablet, such as pediatric, geriatric patients and psychiatric patients.
- Convenience in administration of drug and accurate dosing as compared to liquid formulations.
- Water is not required for swallowing the dosage form, which is convenient feature for patients who are traveling and do not have immediate access to water.
- Good mouth feels property helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.
- Fast dissolution of medicament and absorption which will leads to rapid, onset of action.
- Some drugs are absorbed from the mouth pharynx and oesophagus as the saliva passes down into the stomach, in such cases bioavailability of drugs is increased.
- It provides advantages of liquid formulations in the form of solid dosage form.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.[15][16]

Disadvantages

- Since sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.

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- Although this site is not well suited to sustained-delivery systems.
- Sublingual medication cannot be used when a patient is uncooperative or unconscious.
- 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.[17][18]

Table 1: Drugs used in sublingual tablets

Drug	Category	Dosage form
Captopril	Antihypertensive agent	Tablet
Furosemide	Diuretic	Tablet
Scopolamine	Opioid analgesic	Spray
Ondansatron Hcl	Antiemetic	Film
Salbutamol sulphate	Antiasthmatic agent	Film

Table 2: Excipients used in sublingual tablets

Excipients	Uses
HPMC	Tablet binder, Stabilizing agent.
Lactose Monohydrate	Diluent, Tablet binder
Crosspovidone	Superdisintegrant
Cross carmellose sodium	Superdisintegrant
Sodium starch glycolate	Superdisintegrant

HISTORICAL DEVELOPMENT OF SUBLINGUAL TABLETS

Difficulty in swallowing (Dysphagia) is a common problem in all age groups, especially the elderly and pediatrics, because of physiological changes associated with these age groups. It is common to see those afflicted carrying a small device with them, which is used for crushing tablets, enabling easy ingestion. Other categories that experience problems using conventional oral dosage forms include are the mentally ill, uncooperative and nauseated patients, those with conditions of motion sickness, sudden episodes of allergic attack and coughing. Sometimes, it may be difficult to swallow conventional products due to unavailability of water. These problems

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led to the development of a novel type of solid oral dosage form called mouth-dissolving tablets, which disintegrate and dissolve rapidly in saliva without the need of the water. They are also known as fast dissolving tablets, melt-in-mouth tablets, rapimelts, porous tablets, oro-dispersible, quick dissolving or rapidly disintegrating tablets.[19] Table no.3 indicates the contribution of various researchers in the field of sublingual tablets and the table no. 4 indicates the patented technology in the field of sublingual technology.

Table 3 : Contribution in the field of Sublingual Medications

S.No.	Year	Contribution
1.	1986	Freeze drying process converts the mixture of active water dispersible carrier materials into open matrix network that disintegrates rapidly.[20]
2.	1994	Regular compression method that produces tablet with higher mechanical strength.[21]
3.	2001	Formulation and optimization of captopril sublingual tablet using d-optimal design.[22]
4.	2003	In vitro and in vivo evaluation of a new sublingual tablet system for rapid Oromucosal absorption using fentanyl citrate as the active substance.[23]
5.	2006	Formulation and optimization of sublingual tablets of rabeprazole sodium.[24]
6.	2009	Development and optimization of a sublingual Tablet formulation for physostigmine salicylate.[25]
7.	2011	Sublingual route for the systemic delivery of ondansetron.[26]
8.	2012	Formulation and in-vitro evaluation of fast disintegrating Rosiglitazone sublingual tablets.[27]
9.	2012	formulation and evaluation of sublingual tablets of losartan potassium.[28]
10.	2012	Development and characterization of sublingual tablet of lisinopril.[29]
11.	2013	formulation and evaluation of immediate release tablets of linezolid.[30]

Table 3: Patents of Sublingual Medications

Patent No.	Title	Inventor	Assignee	US Classification
US3428728	Timed release sublingual medications	Paul Meredith Terrill	Eli Lilly and Company	514|509
US3873727	Stabilization of molded sublingual nitroglycerin tablets	Paul Meredith Terrill	Eli Lilly and Company	514|509

Method of preparation of sublingual tablets:

Various techniques can be used to formulate sublingual tablets. Direct compression 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

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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 disintegrats, 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. (20)

DIRECT COMPRESSION

Processing steps are:

Raw material → weighing → screening → Mixing → Compression.

Direct compression consists of compressing tablets directly from powdered materials without modifying physical nature of materials. This method is applicable for crystalline chemicals having good compressible characteristic and flow properties such as: Potassium salt (chlorate, chloride, bromide), Sodium chloride, Ammonium chloride, Methenamine etc. If necessary, direct compression vehicles can be used which are having good flow and compressible characteristics. Commonly used directly compression diluents are: MCC (Microcrystalline cellulose (Avicel), Spray dried lactose, Starch - (Sta Rx 1500, Embdex, Celutab), Sugar (Sugartab, Nutab), Dicalcium phosphate dihydrate (Di-Tab), Mannitol for chewable tablet.(16)

Advantages

1. Low labor input
2. A dry process
3. Fewest processing steps (17)

Disadvantages

1. Stratification may occur due to differences in particle size and bulk density which results poor content uniformity.
2. 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.
3. During handling of dry materials static charge may form which may present uniform distribution of drug.
4. Direct compression diluents may interact with the drug. For example, amine drug with Lactose produce discoloration of tablet. (!8)

Evaluation parameter:

To design tablets and later monitor tablet production quality, quantitative evaluations and assessments of tablets chemical, physical and bioavailability properties must be made. Not only could all three property classes have a significant stability profile may be interrelated i.e., chemical breakdown or interactions between tablet components may alter physical tablet properties, greatly changing the bioavailability of a tablet system.

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General appearance

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Include in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking. (19)

Uniformity of weight

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. (20)

Table 3: Pharmaceutical Limits For Weight Variation (Indian Pharmacopoeia)

Average wt of tablets	% variation allowed
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250 mg or more	5

Hardness and thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer. Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester. (19)

Friability

It is measured of mechanical strength of tablets. Roche friabilator can be used to determine the friability by following procedure. A preweighed tablet was placed in the fribaiator. Fribaiator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabalator for at least 4 minutes. At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as

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

Wetting time (WT)

A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time

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for complete wetting was measured. Three trials for each batch and the standard deviation were also determined.

Water absorption ratio

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. [22]

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. [23]

Drug Content

Randomly ten tablets are selected from formulation, finely powdered and powder equivalent mg of drug is accurately weighed and transferred to 100 ml 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. [24]

***In-vitro* dissolution studies**

Dissolution study was carried out in USP paddle type apparatus using 300 mL of stimulated salivary fluid (pH 6.8) as a dissolution medium at 50 rpm. Temperature of the dissolution medium was maintained at 37±0.5ºC. Samples of 5ml were withdrawn at every 4 minute interval, filtered (through 0.45µ) and replaced with 5ml of fresh dissolution medium. The samples were suitably diluted and estimated spectrophotometrically at 276 nm by using ELICO-164 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. [26]

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Table 3: Marketed Products of Sublingual Tablet

Brand name	Drug	Category
Abstral	Fentanyl Citrate	Opioid analgesic
Edular	Zolpidem Tartrate	Sedatives/Hypnotics
Avitan	Lorazepam	Antianxiety
Subulex	Buprenorphine	Opioid analgesic
Nitrostat	Nitro-glycerine	Antianginal
Suboxone	Buprenorphine	Narcotic+Opioid antagonists
Isordil	Isosorbide Dinitrate	Vasodilators

CONCLUSION

Recently 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. Peak blood levels of most products administered sublingually are achieved within 10-15 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. Various types of sublingual dosage forms are available in market like tablets, films and sprays.

FUTURE PROSPECTS

Sublingual tablets are one of the most suitable candidates for the oral delivery of drugs such as proteins and peptides that have limited bioavailability when administered by conventional tablet. Injections generally are not favored for use by patients unless facilitated by sophisticated auto-injectors. The developments of enhanced oral protein delivery technologies by ODTS which may release these drugs in the oral cavity are very promising for the delivery of high molecular weight proteins and peptides.

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