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FORMULATION AND EVALUATION OF KETOTIFEN FUMARATE SUBLINGUAL TABLET

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Abstract:-

Ketotifen fumarate is the fast disintegrating tablet. KF is a second -generation H1 Antihistamine and mast cell stabilizer. Ketotifen has antiallergic activity. Sublingual drug delivery can be alternative and better route as compared to oral drug delivery as sublingually administered dosage forms bypass hepatic metabolism. It show rapid onset of action therefore used in the treatment of acute disorder. Sublingual tablet disintegrated rapidly and small amount of saliva is sufficient for achieving disintegration of dosage form coupled with better dissolution and increase bioavailability. The Sublingual tablet of ketotifen fumarate was prepared by wet granulation method using active ingredient is ketotifen and excipients are microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, anhydrous colloidal silicon dioxide, magnesium stearate, sucrose, sodium benzoate and titanium dioxide. Pre-formulation study of sublingual tablet such as melting point, solubility, bulk density, tapped density, angle of repose, carr's index and Haunser ratio. The tablet are evaluated for post-compression parameters like general appearance, uniformity of tablet weight, hardness and thickness, wetting time, water absorption ratio, friability, disintegration and dissolution.

Keyword: mouth dissolving, Ketotifen fumarate, fast disintegration, wetting time, increase bioavailability, allergic condition.

INTRODUCTION :-

Asthma is characterized by increased responsiveness of trachea and bronchi to various stimuli and by narrowing of the airways. The highly vascularized cheek mucosa absorbs substances. Directly into the bloodstream Resulting in systematic delivery [1].It is one of the most common chronic diseases in the world. It is characterized by bronchial hyperresponsiveness and reversible airflow restriction. Asthma can be classified by phenotype into allergic, non-allergic, childhood, slow onset, obese, occupational. Severe asthma and asthma with constant airflow obstruction in the elderly and asthma [2,3,4,5].It recognize in many cultures like Chinese, Hebrews, Greek and Roman. The World asthma day is celebrated on 6 May, To increase awareness and improve care for people with asthma. first time respiratory distress was recorded in China in 2600BC. The evidence found in the form of 'Noisy breathing'. Hippocrates was first person who found that people suffering from asthma may have hunch back Over 2000 years. Ketotifen used to treat
asthma, allergic condition indition and chronic obstructive pulmonary disease. According to the
WHO, in 2019, approximately 262 million people were affected and 461,000 people died. It is estimated that

approximately 300 million people worldwide have asthma, and there will be

approximately 100 million people with asthma by 2025. The severity, prevalence, and mortality of asthma varies greatly geographically. The asthma patients is more than the HIV and Tuberculosis disease. The patient's head increased due to pollution. Environmental allergies (such as dust, animal hazards, and mold), obesity, viral infections, cigarette smoke, occupational exposures (chemicals, fumes, dust), lifestyle, hormone replacement therapy. Ketotifen is non – specific mast cell stabilizer, prevent asthma by H1 receptor antagonist, phosphodiesterase inhibit and result into acculturation of cyclic adenosine monophosphate (cAMP), inside the cells, inhibit the release of inflammatory mediators slow reacting substance of anaphylaxis (SRS) and inhibit calcium flux in bronchial smooth muscle. Fumarate salt is used to improve stability and bioavailability ketotifen. Pharmacological action of ketotifen fumarate-

1. Antihistamine activity
2. Mast cell stabilization
3. Anti-inflammatory effect

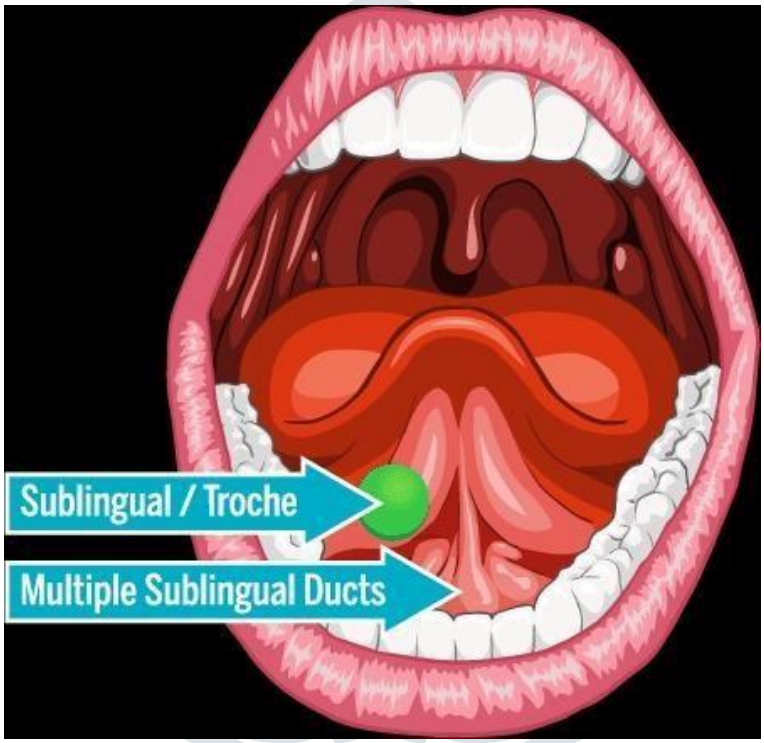

Fig.Sublingual route

SUBLINGUAL TABLET :-

Sublingual tablets are a form of oral medication. Which quickly dissolves under the tongue By releasing active ingredients for rapid absorption into the bloodstream through the mucous membrane. The buccal mucosa is less permeable than the sublingual mucosa. The sublingual route has general advantages. Other delivery routes include the nasal, pulmonary, oral, and subcutaneous systems. Characters – a) small size and weight b) flat or rounded shape c) fast dissolving time (1-3) minute d) rapid absorption by passing first pass metabolism e). local and systemic effect .The buccal tablet is absorbed directly in the blood stream and result in systemic delivery.

1. Drug used for sublingual administration –

Sublingual drug delivery used to treat barbiturates, enzymes, hormones, and certain cardiovascular diseases [6.] The administration of multiple vitamins and minerals is a growing field and the ins and outs of this method are quickly and comprehensively absorbed. Nutrition benefits for sublingual absorption Provides direct nutritional benefits without coming into contact with the stomach or liver[7].This is beneficial for people with digestive

issues, ulcers, coeliac disease, hyperactive gut, elderly people and invalids.

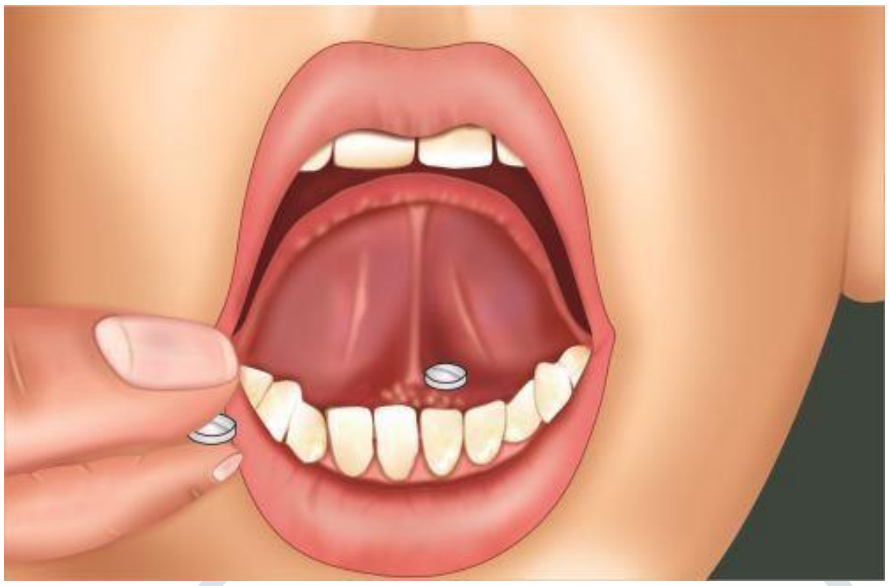

Fig.Administration of Sublingual tablet

2. Absorption of sublingual tablet –

Local dialect meaning 'under the tongue' refers to giving a substance by mouth so that the substance is absorbed more quickly through the sublingual blood vessels than through the sublingual channels. Absorption allows highly intravascular oral mucus to more directly reach the blood flow. Therefore directly causing the system. This is the area of heart medicine, steroids, barbiturates, and certain enzymes. Therefore it is appropriate. The administration of many vitamins and minerals which are found to be readily and thoroughly absorbed by this method [8,9]. The mucosa functions primarily as a barrier-similar to skin. It was once believed that the barrier of human skin was 'impenetrable' (e.g., Vitamins E and C creams, hormones, nicotine patches) but still it is a growing field of Administration of sublingual tablet show pharmacological action after only 1-2 minutes'.

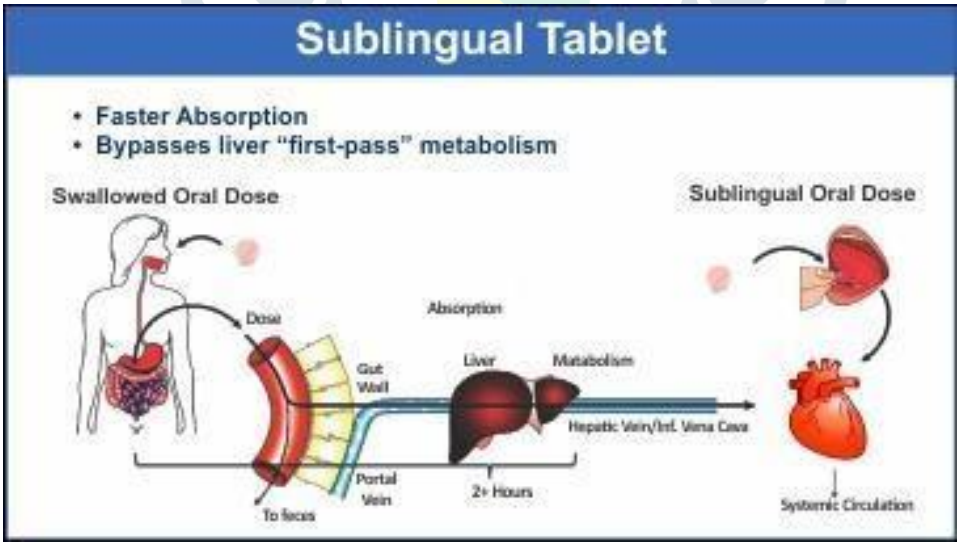

Fig. Absorption of Sublingual drug Ideal properties of drug sublingual drug delivery system:- [10]

- Drug should not bitter flavor.
- Lower dose than 20 mg like Nifedipine.
- Low to intermediate molecular weight.

- Excellent stability in water and saliva.
- PH is partially non-ionized in oral cavity.
- Undergo first pass effect such as ketotifen fumarate.
- Performance of sublingual tablet is affected by many pharmacological qualities such as solubility, crystal shape, particle size, hygroscopicity, bulk density and compressibility.
- Drug preparation are parentally unstable can taken sublingual.

Factors affecting on Sublingual absorption – 1)Lipophilicity of the drug [11]

Complete absorption of the drug through the tongue. The drug must have slightly greater lipid solubility than Gl bioavailability, which is required for slight passive penetration.

2) Oral mucosa Thickness :[12]

The thickness of the sublingual mucosa is 100-200µm which is less as compared to the buccal epithelium. The epithelium under the tongue becomes thinner. Therefore, the absorption of the drug is faster and the drug is released in smaller quantities.

3) pH and PKa of saliva:[13]

Saliva has an average pH of 6.0, which makes it poorly absorbed but still condenses. Moreover, drug absorption through the oral mucosa occurs only when pka is greater than 2 for acids and less than 10 for bases.

4) Drugs that adhere to the oral mucosa have poor/poor systemic availability.[14]

5) Partition coefficient from oil to water:[15]

Compounds with a good oil-water partition coefficient are immediately absorbed through the oral mucosa. The oil-water partition coefficient is in the range of 40-2000, which is considered optimal for drug absorption.

6) Saliva dissolves:

In addition to high fat solubility, The medicine must be soluble in an aqueous oral liquid. This means that biphasic drug solubility is essential for absorption.

7) Adhesions in the oral mucosa:

Drugs that adhere to the oral mucosa have poor/poor systemic availability.

8) Surface area and contact time:

Increased surface area and contact time enhance absorption.

9) Formulation factors:

- Tablet or solution composition.
- Excipients and their concentrations.
- Manufacturing process.

Advantages – [16,17,18]

- It has quick action as compared to the oral cavity
- Liver is bypassed and also drug is protected from metabolism due to digestive enzymes of the middle gastro

intestinal tract.

- Improved patient compliance due to the elimination of associated pain with injections.
- Low dosage provides high efficiency. This is because it avoids liver metabolism in the first place. And the risk of side effects is reduced.
- The large contact surface of the oral cavity facilitates rapid and extensive drug absorption. Works quickly These sublingual dosage forms are widely used in emergency situations such as asthma.
- Rapid absorption and high blood levels due to high blood vessel presence in the area. Therefore, it is very useful in giving anti-atherosclerotic drugs.
- It also has the advantage of being able to quickly decompose or dissolve in the mouth, Without using water or chewing food.

Disadvantages –[19]

- Because sublingual administration interferes with eating, drinking, and talking, it is generally considered unsuitable for long-term administration.
- This site is not suitable for a sustainable distribution system, though
- Sublingual drops cannot be used if the patient is uncooperative.
- Patients should not smoke while taking sublingual lozenges. Because smoking causes the blood vessels to shrink. This reduces the absorption of the medicine.
- There are many different types of sublingual lozenges available, but tablets, films and sprays are the current trend. Various methods for preparing these dosage forms are described according to their feasibility and advantage. Above other methods
- In any case, tooth stains are formed and are caused by prolonged use of this technique on acids or burns in general.

Application –

1) 1.Allergy relief
2) 2. Asthma prophylaxis
3) Cardiovascular disease
4) Pain management
5) Anxiety and depression
6) Hormone replacement therapy
7) Migraine treatment

MATERIALS AND METHOD :-

Materials –

Sr. no	Materials
1	Ketotifen fumarate
2	Microcrystalline cellulose
3	Sodium starch glycolate
4	Lactose monohydrate
5	Hydroxypropyl cellulose
6	Magnesium stearate
7	Sucrose
8	Cherry
9	Titanium dioxide

Procedure – [20]

Formulation of ketotifen fumarate sublingual tablet by wet granulation technique -

- Ketotifen fumarate is added to the granulator. And the starch is mixed in a blender by adding aerobic excipients such as lactose monohydrate, hydroxypropyl cellulose, sodium starch glycolate.
- Add a granulating liquid such as alcohol or ethanol to the powder to create a wet mass of powdered material.
- This mass passes a to form granules or pellets. Currency number 20-30(#20-30).
- The granules are dried to reduce the moisture content. Using hot air over a liquid dryer or sunlight.
- After drying The granules pass through sieve number 40 to 60 to obtain granules with uniform particle size, which are used for smooth granulation compression.
- Then add magnesium stearate and mix in a blender.
- These granules are then compressed using mechanical tools. (Punch diameter 6-8 mm and die diameter 7-9 mm) of tablet compression.
- Maybe it's the coating that is. Titanium dioxide is used to mask the taste of medicine.

PREFORMULATION STUDY :

Pre-formulation study of tablet determined by flow and compressibility.

1. **Melting point:-[21,22]**

It gives the information regarding the purity of a compound. The substance whose melting point was determined dried and introduced into a small dry capillary tube, then sealed at one end so as to form a compact column. The capillary is tied to a thermometer, introduced in the Thiele's tube and heated the tube up to the melting then note the thermometer reading.

2. **Solubility:-**

To check the drug which is soluble in water or liquid phase. The solvents are included such as water, ethanol and methanol.

3. **Bulk density:[-23,24]**

Density is defined as weight per unit volume. Bulk density is defined as the mass of the powder divided by the bulk volume. It is expressed as gm/ ml.

$$\text{Bulk density} = \frac{\text{Weight}}{\text{Bulk volume}}$$

4. **Tapped density:-**

Tapped density was obtained by dividing the mass of powder by the tapped volume in ml. The sample of the powder is introduced in the granulate cylinder then tapped the cylinder 100 times then divide the weight of sample in gm by the final tapped volume in ml of sample contain cylinder.

5. **Angel of repose: [25]**

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

Tan (θ) =h/r

Relation between angel of repose and flow of particles

Angle of repose	Flow
< 25	Excellent
25-30	Good
30-40	Passable
>40	Poor

6. Compressibility index:-

It is also called as carr's index.

Measure powder compressibility and flowability.

Carr's index = tapped density – bulk density
Tapped density

7. Haunser ratio:-

Haunser ratio is defined as, the ratio of tapped density to the bulk density.

VALUATION OF SUBLINGUAL TABLET :-

1. General appearance:

The general appearance of tablets is identity and overall elegance is essential for the consumer acceptance for the production process. General appearance includes character such as size and shape of tablet, colour, presence or absence of odour, taste, surface texture physical flow and consistency directly identifying market.

2. Uniformity of tablet weight: [26]

According to IP, the weight of twenty tablets has determined individually and collectively on digitally weighing balance. Then calculate average weight of one tablet was calculated.

3. Hardness test: [27,28]

Hardness test is measured by Monsanto hardness tester. The tablet is breaking under the storage condition and handling before the use depend on hardness. It is measured to determine the need for adjustment of pressure for compression.

4. Thickness test: [29,30]

Thickness is measured by using Vernier caliper or Screw gauge. Tablet thickness should controlled within ± 5 % variation of standard value.

5. Friability test: [31]

Friability will be measured by taking randomly 10 tablets which is weighed, placed in a Friabilator (Roche Friabilator) dropping tablet at height or distance 6 inch and rotated at 25rpm for a period of 4 minutes. After the test weight the tablet powder or dusted and percentage friability was calculated

$$\% \text{ Friability} = \frac{\text{initial weight - final weight}}{\text{Initial weight}} \times 100$$

6. Wetting time: [32]

The tablet was placed at the Centre of two layers of absorbent paper fitted into a dish. After the paper was thoroughly wetted with saline phosphate buffer (pH-6.8), excess water was completely remove from dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch.

7. Water absorption ratio: [33]

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of saline phosphate buffer (pH- 6.8). A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighted. Water absorption ratio, R was determined using following equation.

$R=100\ (Wa–Wb)/Wb$

Where,

R = water absorption ratio

Wa = weight of tablet after water absorption Wb = weight of tablet before water absorption.

8. In-vitro disintegration time:- [34,35]

Disintegration times for sublingual tablets were determined using USP, tablet disintegration apparatus with saline phosphate buffer of pH 6.8 as medium. Maintained the medium temperature at 37 ± 2 °C. The time in minute taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured.

9. Dissolution test: [36,37]

Dissolution studies were performed in a slipper type instrument using 300 mL of activated saliva (pH 6.8) as the dissolution medium at 50 rpm. The temperature of the dissolution medium was maintained at 37±0.5°C. Therefore, the samples were diluted and ca. Spectrophotometric value Solubility studies were performed in triplicated.

Conclusion:

The studies of sublingual tablets have proven that patient compliance is improved. And it's a better way to manage medications for both young and elderly patients. Sublingual drug delivery has been used to manufacture many drugs. Especially drugs that must act quickly. The target population has also expanded to those who want convenient pills that do not require water. The drug content in the tablet enters the systemic circulation through the sublingual capillaries. The sublingual dosage form not only improves patient compliance; But it also reduces the time it takes to start responding to treatment. And increases the bioavailability of the drug compared to traditional oral medications of the Tablets.

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