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Lozenges formulation and evaluation: A review

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Abstract
The administration of drugs through oral route is the most common and the easiest way of administering a drug. However, pediatric, geriatric and bedridden patient's shows inconvenience in swallowing conventional tablets or capsules due to difficulties in swallowing with lesser amounts of water with the medication, unable to tolerate the taste of many drugs when formulated as liquid dosage forms, resulting in poor patient compliance. The medicated lozenges are flavored medicated dosage forms intended to be sucked and hold in the mouth or pharynx. These preparations are commonly used for the purpose of local effect or systemic effect. Advantages of the medicated lozenges as dosage forms include increase in bioavailability, reduction in gastric irritation, bypass of first pass metabolism and increase in onset of action. New drug design to this area always benefits for the patient, physician and drug industry. Medicated lozenges are prepared by heating and congealing method. A medicated lozenge has drawn attention to the researchers as potential drug delivery system and it could be a commercial success in near future.

Keywords: lozenge, troches, excipients, sweeteners

Introduction
Oral drug delivery is the most flavored route for the administration of various medications and tablets are the most widely accepted dosage form. Solid dosage forms are popular because of the ease of administration, accurate dosage, self-medication, pain avoidance, and most importantly patient compliance. Among the major problems faced by many patients with conventional tablet dosage form is difficulty in swallowing. This problem is more apparent when drinking water is not easily available to the patient taking medicine. Dispersible tablet delivery system is characterized by fast disintegration, quick dissolving, rapid release and improved patient compliance. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially the elderly and pediatrics, because of physiological changes associated with those groups.

Historical Names of Lozenges

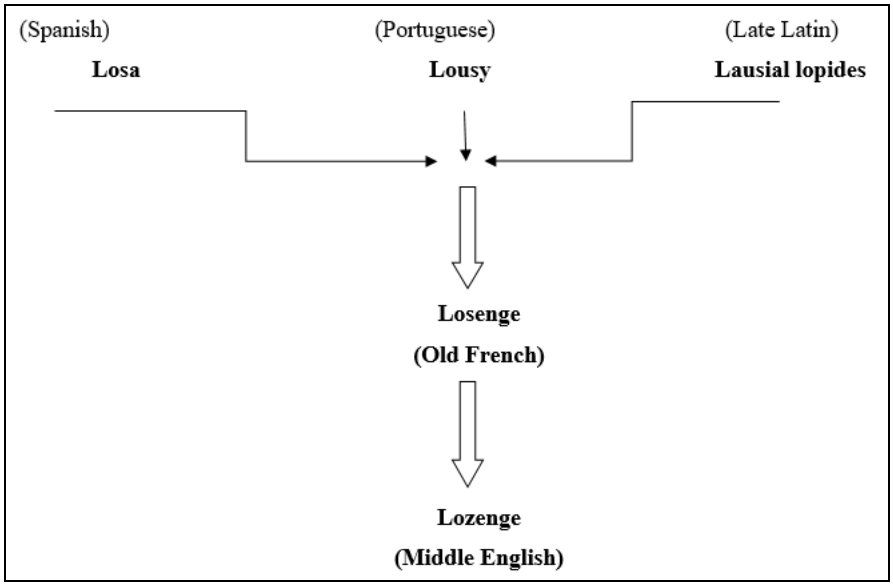

Fig 1

Definition

Lozenges are various-shaped, solid dosage forms usually containing a medicinal agent and a flavoring substance, intended to be dissolved slowly in the oral cavity for localized or systemic effect. They are also called troches or pastilles [2]. (OR) Lozenges are solid & flavored medicated lozenges forms united to be sucked & held in mouth or pharynx. [2]

Advantages

- Ease of administration to pediatrics and geriatrics patients.
- Local and systemic effect through oral cavity.
- Increased contact time of drug.
- Avoid first pass metabolism of drugs.
- Do not require water for intake.
- Suitable for patients having difficulty in swallowing (dysphasia).
- Lozenge is withdrawn if dose is not needed.
- Less production time.
- Cost of production is less.
- Provides flavor and pleasant taste in mouth.
- Better patient compliances.

Disadvantages

- Non-ubiquitous distribution of drug in saliva for local therapy.
- Possible draining of drug into the stomach.
- Accidental swallowing of entire dosage form.

Types of lozenges

Table 1

Antifungal Lozenges
Nicotine Lozenges
Zinc Lozenges
Throat Lozenges
Morning Sickness Lozenges

Types

Lozenges are various-shaped, solid dosage forms usually containing a medicinal agent and a flavoring substance, intended to be dissolved slowly in the oral cavity for localized or systemic effect. They are also called troches or pastilles. Pastilles have a softer texture and a high percentage of a sugar or a combination of a gelatin and sugar. Many lozenges have hard candy bases of sugar and syrup and often incorporate an adhesive substance such as acacia. Commercial lozenges (troches) may be made on a tableting machine using high compression pressures. Lozenges are designed to dissolve slowly in the mouth. They are designed to dissolve and not to disintegrate. Ingredients should be heat-stable if they are to be incorporated into extemporaneously-prepared lozenges. Recently, soft lozenges and chewable lozenges have been re-introduced into pharmacy and are enjoying increased popularity. The soft lozenges generally have a polyethylene glycol base and the chewable lozenges have a glycerinated gelatin base. These usually are chewed and are a means of delivering the product to the gastrointestinal tract for systemic absorption. [16-20]

Hard candy Lozenges

Hard candy lozenges are mixtures of sugar and other carbohydrates in an amorphous (no crystalline) or glassy condition. These can be considered solid syrups of sugars and Lozenges historically have been used for the relief of minor sore throat pain and irritation and have been used extensively to deliver topical anesthetics and antibiotics. Lozenges are various-shaped, solid dosage forms usually containing a medicinal agent and a flavoring substance, intended to be dissolved slowly in the oral cavity for localized or systemic effects. Usually, they have a moisture content of 0.5 to 1.5% Hard lozenges should provide a slow, uniform dissolution or erosion over 5 to 10 minutes, not disintegrate, have a smooth surface texture and have a pleasant flavor masking the drug taste. A primary disadvantage of hard candy lozenges is the high temperature required for their preparation. Hard candy lozenges generally weigh between 1.5 to 4.5 gm. Excipients such as sorbitol and sugar have demulcent effects, which relieve the discomfort of abraded tissue resulting from irritation due to cough and sore throat. A portion of the active drug product actually may be absorbed through the buccal mucosa, thereby escaping the first-pass metabolism which occurs when a drug is swallowed and absorbed through the gut. [11-12]

Soft Lozenges

Soft lozenges have become popular because of the ease of extemporaneous preparation and applicability to a wide variety of drugs. The bases usually consist of a mixture of various polyethylene glycols, acacia or similar

materials. One form of these soft lozenges is the pastille, which is defined as a soft variety of lozenge, usually transparent, consisting of a medication in a gelatin, glycerogelatin or acacia: sucrose base. Pastilles may be colored and flavored and can be either slowly dissolved in the mouth or chewed, depending upon the action desired for the particular incorporated drug. Soft lozenges are similar to a historical form of medication that is making a comeback: the "confection". Confections are defined as heavily saccharimeter, soft masses containing medicinal agents. The improvement in their current use is largely due to the use of polymers (polyethylene glycols) as the matrix for the dosage form. They are easy to use, convenient to carry, easy to store (room temperature), and are generally pleasant tasting. Polyethylene glycol-based lozenges may have a tendency to be hygroscopic and may soften if exposed to high temperatures. Consequently, storage in a cool, dry place should be recommended. [8-9]

Chewable Lozenges

Soft, chewable candies have been on the market for a number of years. They are very highly flavored and many often contain a slightly acidic taste. They are an excellent way of administering drug products as the taste of the drug often can be masked very effectively with fruit-flavored products. They are relatively easy to prepare extemporaneously. The most difficult part involves the preparation of the gelatin base which is described below. These are especially used for pediatric patients and are a very effective means of administering medications for gastrointestinal absorption and systemic use. One of the more popular lozenges for pediatric use is the chewable lozenge, or "gummy-type" candy lozenge. The gelatin base for these chewable lozenges is similar to the former Glycerin Suppositories, or Glycerinated Gelatin Suppositories, which consisted of 70% glycerin, 20% gelatin and 10% purified water. Some of the earlier pastilles consisted of a gelatin or a glycerogelatin base. [8, 9]

Hard Candy Lozenges

Raw Materials

The types of raw materials used in medicated lozenges may vary according to a number of factors. Most medicated lozenges contain sugar, corn syrup, acidulant, colorant, flavor, and the medicament.

1. Sucrose

Sucrose, a disaccharide of glucose and fructose, is obtained from sugarcane or beet. The choice of beet or cane sugar is based on availability and geographical considerations. Sucrose and sucrose products are used in medicated lozenges because of their value as neutral sweeteners, their ready solubility, and their function as a ''drier'' to reduce the weight of the confection through crystallization.

2. Invert sugar

Invert sugar, derived from sucrose, possesses the very desirable physical property of controlling the crystallization of concentrated sugar solutions and maintaining freshness of the finished product through its humectant's properties.

3. Corn syrup

Corn syrup is used in almost every type of confection to control sucrose and dextrose crystallization, which may lead to crumbling. Corn syrup in appropriate proportion with sucrose and dextrose allows the formation of an amorphous glass and produces a candy with the desirable appearance.

4. Isomalt

Isomalt is an almost equimolar mixture of 6-glucopyranosyl-sorbitol (6- GPS) and 1-glucopyranosyl-mannitol (1-GPM), and the weight percentage can vary between 43 to 57% of 6-GPS to 57% to 43% of 1-GPM. Isomalt has properties like a binding agent, i.e., to a certain extent it is capable of establishing binding between the individual particles in the composition and further in the binding during the kneading step in the process of preparing a lozenge. Isomalt is beyond being a binding agent also a suitable softener. The lozenges prepared with a binding agent comprising isomalt are softer than lozenges that do not contain any isomalt.

5. Colorants

Colorants are incorporated into medicated lozenges for appearance, product identification, and masking of physical degradation.

6. Dyes and other organic colorants

Dyes and other organic colorants may degrade by heat or light via oxidation, hydrolysis, photo oxidation, etc., and their compatibility with drug, excipients, and process conditions should be studied before selection. Suppliers of colors are excellent sources of information on current regulatory status of colorants.

7. Acidulants

Acidulants are generally added to medicated lozenges to fortify and strengthen their flavor profile. Organic acids such as citric, malic, fumaric and tartaric acids are most commonly used. Citric acid alone or in combination

with tartaric acid is the most common. Another use of acids in medicated lozenges is to alter the pH to maintain the integrity of the drug.
Regular conversion corn syrup has a pH of 5.0–6.0. Addition of a weak organic acid to improve flavor lowers it to 2.5–3.0, a pH at which some medicaments exhibit maximum stability. If necessary, some drugs can be stabilized by adjusting the pH to 7.0–8.0 with a suitable weak base such as calcium carbonate. (8-9)

8. Flavors
Flavors used in medicated lozenges must be compatible with the drug and excipients and capable of withstanding the rigors of the manufacturing conditions.
Flavors consist of numerous chemicals that may interact with excipients or medicaments and that degrade by heat and light. Aldehydes, ketones, and esters may react with drugs. A classic example of flavor–drug interaction is that of a primary amine drug (benzocaine, phenylpropanolamine) with aldehyde containing flavor components like cherry, banana, etc (8-9)

9. Salvage
The last major ingredient in lozenges is salvage obtained from lozenge batches rejected because of imperfect shape or size, presence of air bubbles, or unacceptable drug concentration. Salvage, if properly heated, can be reused in finished products without altering color, texture, lozenge base composition, or drug concentration. Before any salvage can be used as part of a medicated lozenge base, it should be adjusted to a pH of 4.5–7.5 to prevent excessive and uncontrolled formation of reducing sugars, and the stability of the drug at cooking cycles should be determined. [8-9]

Candy-Base Manufacturing
The first step in the manufacture of medicated lozenges is the preparation of candy base, followed by the addition of medicament, flavor, acidulants, colors, etc., and finally by lozenge formation. Irrespective of process, the manufacture of medicated lozenges involves the cooking of candy base, mixing, batch forming, ‘‘rope’’ sizing, adjustment of weight, lozenge formation, cooling, and storage of lozenges. [8-9]

Compressed Tablet Lozenges
Commercially, the preparation of lozenges by tablet compression is less important than hard-candy manufacturing techniques. Essentially, lozenge tablets differ from conventional tablets only in their organoleptic and non-disintegrating properties and slower dissolution rate.
The associated attributes of pleasant taste with or without matching color, smoothness, and mouth feel during prolonged dissolution on the tongue, and the physical consideration of holding the tablet in the mouth while swallowing its dissolved components,
Unusual formulation requirements are to be met by lozenges compared to those of tablets intended for swallowing or chewing. The commonly used drugs mentioned previously tend to be bitter, unpleasant tasting compounds. The desire to release these agents slowly in the mouth, in constant contact with the tongue, demands a formulation approach unlike that found in any other dosage form. [11-14]

Processing and Excipients
Any of the common tablet-processing methods, such as wet granulation, dry granulation, or direct compaction, may be utilized in the production of lozenge tablets. However, because the tablets should dissolve very slowly without disintegration, wet granulation is preferable because it generally provides better control. Through the judicious use of wet binders that retard dissolution, it should be possible to design a formulation having the appropriate dissolution rate.
Formulating for slow dissolution, plus smoothness and good mouth feel, these require careful excipient selection and appropriate process development to ensure that the controlling variables are dealt with correctly. Several important aspects of lozenge tablet manufacture are critical to all of the desired performance attributes of the finished product. These include assurance of necessary particle size and distribution, maintenance of correct moisture content, and achievement of proper tablet hardness. Process development and scale up considerations must be thoroughly explored to ensure the establishment of proper specifications for these parameters. [11-14]

Table 2: Excepients used

Sr. No.	Ingredients	Example
1	a) Sugar b) Sugar free vehicles c) Fillers	Dextrose, sucrose, maltose, lactose. Mannitol, sorbitol, polyethylene glycol (PEG) 600 and 800. Dicalcium phosphate, calcium sulfate, calcium carbonate, lactose, microcrystalline cellulose.
2	Lubricants	Magnesium stearate, calcium stearate, stearic acid and PEG, vegetable oils and fats.
3	Binders	Acacia, corn syrup, sugar syrup, gelatin, polyvinyl pyrrolidone, tragacanth and methylcellulose.
4	Coloring agents	Water soluble and lakolene dyes, FD & C colors, orange color paste, red color cubes,

		etc.
5	Flavoring agents	Menthol, eucalyptus oil, spearmint, cherry flavor, etc
6	Whipping agents	Milk protein, egg albumin, gelatin, xanthan gum, starch, pectin, algin and carrageenan
7	Humectants	Glycerin, propylene glycol and sorbitol.

Flavoring agents Selection

For hard lozenges, the emphasis is on the slow, uniform release of the medication directly onto the affected mucous membrane. This presents an additional challenge to the compounding pharmacist to develop flavor blends that effectively mask any unpleasant principles contributed by the medications, while maintaining a smooth lozenge surface texture as the tablet slowly dissolves. If the incorporated medication has no significant taste, flavoring will not be a problem. However, if the medication has a strong, disagreeable taste, special emphasis should be placed on minimizing the taste in order to enhance patient compliance. Flavor is a very complex phenomenon that is a combination of the senses of taste, touch, smell, sight and sound. The first of these, taste, is made of four primary tastes: sweet, bitter, sour and salty. (11-14)

Table 3: Flavoring agents

Bitter	**SpiceWild Cherry, Licorice, Chocolate Mint,Grapefruit, Coffee, Cherry, Peach,**
Acrid	Raspberry, Orange, Lemon, Lime
Sour	Raspberry, Fruits, Berries, Acacia
Oily	Syrup
Sweet	Peppermint, Anise, Wintergreen
Acrid	Fruit, Berry, Vanilla
Metallic	Citrus Berries, Mint, Grape, Marshmallow

Types of Moulds used for Lozenges

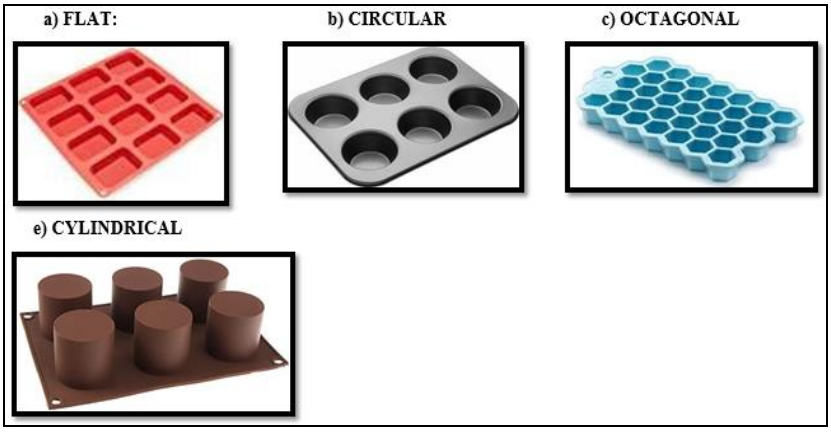

Fig 2

Method of preparation of medicated Lozenges [11-13]

Technique used → heating and congealing.

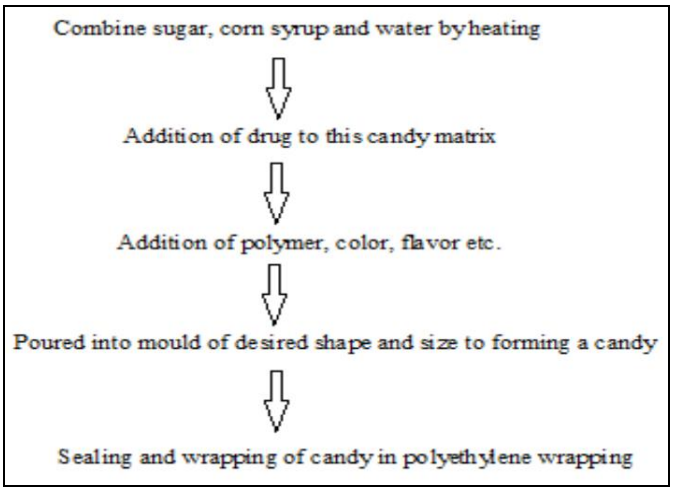

Fig 3

Evaluation of medicated Logenges (20-25)

The prepared lozenges were evaluated for parameters like drug content uniformity, hardness, thickness and diameter, weight variation, friability and in vitro dissolution test, drug content, moisture content analysis and stability [20-25].

Thickness & Diameter

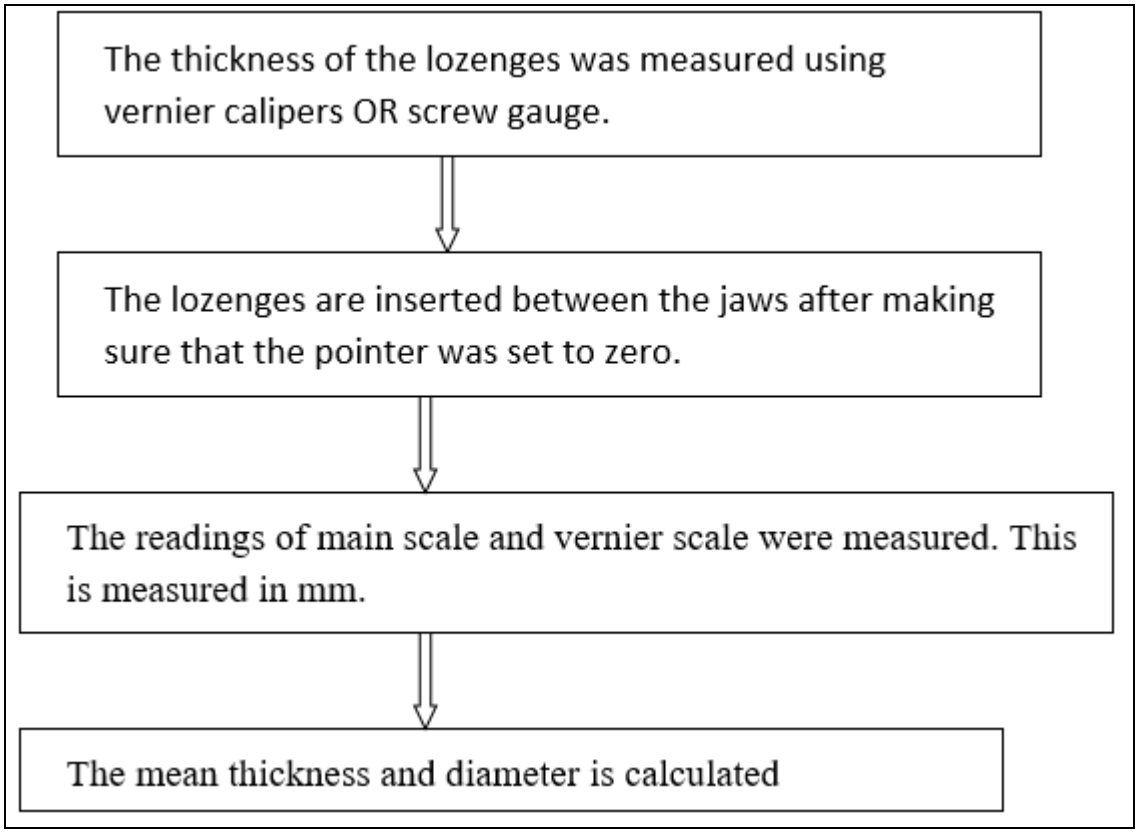

Fig 4

Weight variation

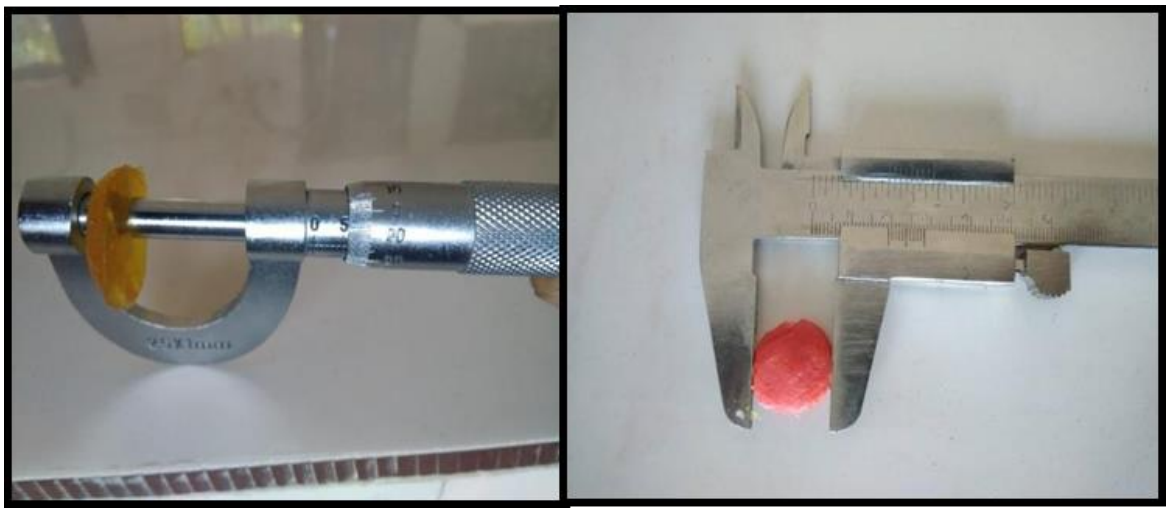

Fig 5

According to weight variation test,
Then the weight variation was calculated

$$\text{Using formula, Weight variation} = \frac{\text{Average weight- initial weight}}{\text{Average weight}} \times 100$$

Friability test

The 20 lozenges were taken on a friabilator and were operated for4 min at 25rpm.

⇩

Than the lozenges were taken after 4min & they were then made free from dust and reweighed.

⇩

Then the percentage friability was calculated and % loss was calculated.

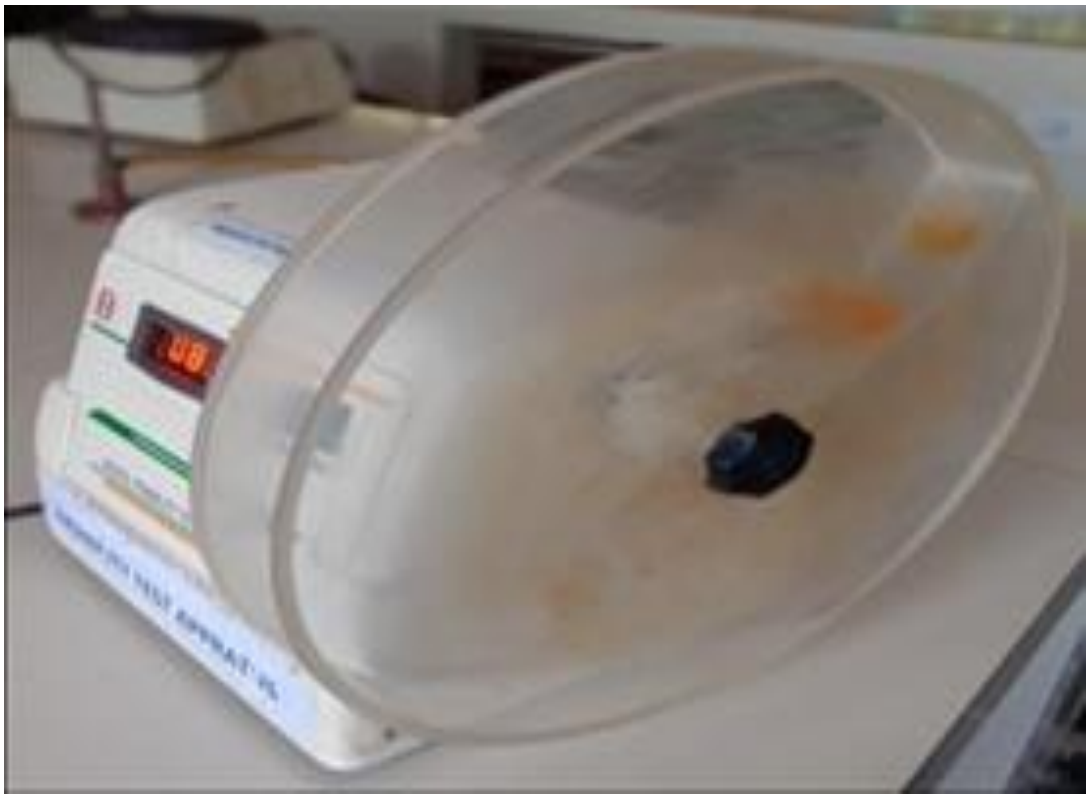

Fig 6

$$\text{Percentage friability} - \frac{\text{Initial Wt- Final Wt}}{\text{Initial Weight}} \text{ X } 100$$

4. Drug content

Appropriate number of lozenges are crushed and dissolved in an appropriate solvent and the absorbance of the solution is measured spectro photometrically.

5. Hardness

The hardness of lozenge was measured using Monsanto Hardness Tester, where the force required to break the lozenge was noted. 3 lozenges were tested.

Monsanto hardness **Tester Pfizer Hardness Tester**

Fig 7

6. Moisture content analysis

Moisture content in the final lozenge was determined by using HELIUM MOISTURE BALANCE apparatus. The sample was weighed & crushed in mortar from that 1gm of sample weight & placed in a desiccator for 24hrs after sample was weighed and moisture content is determined by moisture balance apparatus. Or by abstracting the final weight with initial weight of lozenges.

7. Mouth dissolving time test

The time taken by lozenge to dissolve completely was determined by the USP disintegration apparatus where hard lozenge were placed in each tube of apparatus & time taken for the lozenge to dissolve was noted by using phosphate buffer of PH 6.4 at 370 c. the test was performed 3 times and average dissolving time was calculated and presented with standard deviation.

8. *In vitro* drug dissolution studies

In vitro dissolution studies were carried out using USP dissolution teat apparatus type II (paddle type) at 100 rpm and 37 ± 0.50 c PH 6.8 buffer containing 2% SLS was used as dissolution medium for in *In vitro* dissolution studies. A lozenge was placed in each flask of the dissolution apparatus & samples of 5ml were withdrawn at predetermined time travels for 60minits in order to maintain sink conditions an equal volume of medium was replaced. The sample was analyzed by using UV. Visible spectrophotometer at specific nm & percentage drug released was calculated. This experiment was done in triplicate and the average percentage released was calculated.

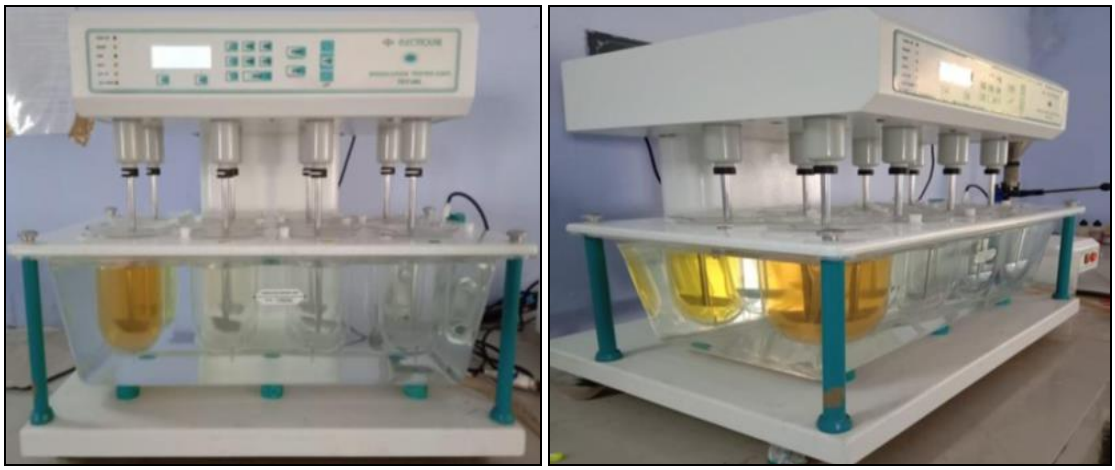

Fig 8

9. Stability study

The stability study was performed to assess physical as well as the chemical stability of the drug, which may possibly affect the organoleptic properties of the lozenges. Accelerated stability study was conducted as per ICH guidelines (zone 4) at 45oC and 75% relative humidity over a period of seven weeks. Sufficient number of optimized formulations were packed in amber colored screw capped bottles and kept in incubator maintained at 37oC. Samples were taken in intervals of 15 days to estimate the drug content and to evaluate organoleptic properties.

10. Microbial check
In this, the presence of any bacterial, mold or spore contamination is checked in raw materials, finished products, machinery, cooling tunnels, environmental conditions and storage drums.

Laboratory microbial testing should include the following counts
- Total plate
- Total coliform
- Yeast and mold
- E. coli
- Staphylococcus
- Salmonella

Storage
These preparations should be stored away from heat and out of the reach of children. They should be protected from extremes of humidity. Depending on the storage requirement of both the drug and base, either room temperature or refrigerated temperature is usually indicated.

Packaging
Since the lozenges are hygroscopic in nature, a complex and multiple packaging is adopted. The individual unit is wrapped in polymeric moisture barrier material which are then placed in tight or moisture resistant glass, polyvinyl chloride or metal container that is over wrapped by aluminum foil or cellophane membrane.

Recent advances
The USP currently recognizes Cetyl pyridinium chloride Lozenges and Nystatine lozenges. Sublingual Zolpidem tartarate lozenge for the treatment of Insomnia was developed. Bacitracin was developed in the form of lozenge for the treatment of infections caused after burns, scars etc.

Nicotine lozenges
These are the newest form of Nicotine replacement therapy on the market. The FDA recently approved he first Nicotine-containing lozenge as an over-thecounteraid in smoking cessation. These are available in 2 strengths: 2 mg and 4 mg

Conclusion
The formulation of lozenges is an easy and time saving process. It is a formulation which is more organoleptically accepted particularly by the pediatric patients. Medicated Lozenges will be ideal dosage forms for pediatric patients. These will have additional advantages of patient compliance, convenience and comfortless for efficient treatment including low dose, immediate onset of action, reduced dosage regimen and economic. This will offer better innovative dosage form. Lozenges enjoy an important position in pharmacy and will continue to remain at the same in future.

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