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REVIEW ON LOZENGES FOR ORAL BACTERIAL INFECTION

Surbhi Choursiya*

Sri Aurobindo Institute of Pharmacy, Indore (M.P.), India.

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ABSTRACT

Oral cavity can be used for local drug delivery as in for periodontitis, dental caries or for oral mucosal drug delivery. This article gives an overview of basic structure, function, biochemistry, and permeability of the oral cavity. Oral drug delivery is the most preferred and convenient option as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs. The oral route of drug administration has been the one used most for both conventional as well as novel drug delivery. The development cost of a new chemical entity is very high the pharmaceutical companies are now focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects. There are many drugs dosage forms like lozenges, tablets, mouthwash and topical gel are in markets for the treatment of oral infection. Lozenges are one of the very popular and better innovative dosage form and oral confectionary products. It is a potentially useful means of administering drugs either locally or systematically via, the oral cavity.

Key words: Gingivitis, Acute necrotizing ulcerative gingivitis, Pharyngitis, Syphilis, Gonorrhea.

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INTRODUCTION

In the recent years scientific and technological advancements have been made in the research and development of oral drug delivery systems. The reasons that the oral route achieved such popularity may be primarily due to its ease of administration. The development cost of a new chemical entity is very high the pharmaceutical companies are now focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects. There are many drugs dosage forms like lozenges, tablets, mouthwash and topical gel are in markets for the treatment of oral infection. Lozenges are one of the very popular and better innovative dosage form and oral confectionary products. It is a potentially useful means of administering drugs either locally or systematically via, the oral cavity. The "lozenges are solid medicated, flavored and sweetened base dosage forms intended to be sucked and hold in the mouth/ pharynx".

Oral cavity

(A) Anatomy and physiology of oral cavity

The oral cavity is lined with mucus membranes with a total surface area of 200 cm^2. The oral cavity has distinct areas:

a. The floor of mouth (sublingual)
b. The buccal area (Cheeks)
c. The gums (gingival)
d. The palatal region (Hard palate and soft palate).

The buccal and sublingual are the commonly used routes for producing local or systemic effects.

(B) Oral mucosa

Structure

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (Fig. 2). Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is

Corresponding Author:- **Surbhi Choursiya** Email:- drx.surbhichoursiya@gmail.com

similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers [1-6].

The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800μm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 μm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosal of areas subject to mechanical stress (the gingivae and hard palate) are keratinized similar to the epidermis. The mucosa of the soft palate, the sublingual, and the buccal regions, however, are not keratinized. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia do not contain acylceramides and only have small amounts of ceramide. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosylceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia.

Structure of oral mucosa

Permeability

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4 - 4000 times greater than that of the skin. As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosae. In general, the permeability of the oral mucosae decreases in the order of sublingual greater than buccal and buccal greater than palatal. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized.

Routes of Drug Absorption through Oral Mucosa

There are two permeation pathways for passive drug transport across the oral mucosa: Para cellular and Transcellular routes. Permeates can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusion. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubility in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds. Since the oral epithelium is stratified, solute permeation may involve a combination of these two routes. The route that predominates, however, is generally the one that provides the least amount of hindrance to passage.

(C) Environment

The oral cavity is marked by presence of saliva produced by salivary glands and mucus which is secreted by major and minor salivary glands as part of saliva.

Role of Mucus

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the principle components of which are complexes made up of proteins and carbohydrates. These complexes may be free of association or some may be attached to certain regions on the cell surfaces. This matrix may actually play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another. Along the same lines, the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems. In stratified squamous epithelia found elsewhere in the body, mucus is synthesized by specialized mucus secreting cells like the goblet cells, however in the oral mucosa; mucus is secreted by the major and minor salivary glands as part of saliva. Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands.

Functions of Mucus Layer

- Protective: Resulting particularly from its hydrophobicity.
- Adhesion: Mucus has strong cohesion properties.
- Barrier: The role of the mucus layer as a barrier in tissue absorption of the drugs and influence the bioavailability.
- Lubrication: Mucus from the goblet cell is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation and solubilization of mucin molecules.

Role of Saliva

Another feature of the environment of the oral cavity is the presence of saliva produced by the salivary glands. Saliva is the protective fluid for all tissues of the oral cavity. It protects the soft tissues from abrasion by rough materials and from chemicals. It allows for the continuous mineralization of the tooth enamel after eruption and helps in remineralisation of the enamel in the early stages of dental caries. Saliva is an aqueous fluid

with 1% organic and inorganic materials. The major determinant of the salivary composition is the flow rate which in turn depends upon three factors: the time of day, the type of stimulus, and the degree of stimulation. The salivary pH ranges from 5.5 to 7 depending on the flow rate. At high flow rates, the sodium and bicarbonate concentrations increase leading to an increase in the pH. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water rich environment of the oral cavity [6].

Physiological Functions of Saliva:

- Modulation of the oral flora.
- Assistance in bolus formation.
- Stimulation of epithelial proliferation.
- Initiation of fat and starch digestion.
- Remineralisation of the teeth with calcium phosphate salts.
- Neutralization of acid in the oral cavity and esophagus.
- Lubrication and cleansing of the oral, pharyngeal and esophageal mucosae.

Oral Bacterial Infections

Oral infections are the infection that occurs in around the mouth. Oral infection is very common they can affect the tongue dorsum, lateral sides of tongue, buccal epithelium, hard palate, soft palate, supragingival plaque of tooth surfaces, subgingival plaque.

Bacteria an important group of microorganisms found in both healthy and diseased mouths. There have been more than 500 types of bacteria found in the mouth. Commensally bacteria are regarded as beneficial by depending against the colonization of invading pathogen. One might think thus suggests that the oral cavity is a relatively easy environment for bacteria to colonize. Moreover, a bacterial accumulation on mucosal surfaces is a major factor in the development of most of the common dental diseases such as gingivitis and periodontal diseases. A bacterial oral infection is bacteria invade the oral cavity (mouth) and cause infection (the harmful growth of microorganisms). However, some do cause disease and produce pathogens in the body that make you sick**.**

This bacterial can be responsible for oral infections as follows:

a) Gingivitis.
b) Acute necrotizing ulcerative gingivitis (trench mouth).
c) Pharyngitis (sore throat) and tonsillitis.
d) Syphilis.
e) Gonorrhea [7,8].

Lozenges

The development cost of a new chemical entity is very high; the pharmaceutical companies are now focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side Effects. There are many drugs dosage forms like lozenges, tablets, mouthwash, and topical gel, are in markets for the treatment of the oral infections. New drug design to this area always benefit for the patient, physician and drug industry is lozenges.

The word "Lozenge" is derived from French word "Losenge" which means a diamond shaped geometry having four equal sides. Lozenges and pastilles have been developed since 20th century in pharmacy and is still under commercial production. Lozenges are solid preparations that are intended to dissolve in mouth or pharynx. They may contain one or more medicaments in a flavored and sweetened base and are intended to treat local irritation, infection of mouth or pharynx and may also be used for systemic drug absorption. They can deliver drug multi directionally into the oral cavity or to the mucosal surface. Lozenges are better innovative dosage form placed in oral cavity. 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 antibacterial. Today lozenges contain different category of medicament as follows: analgesics, anesthetics, antimicrobials, antiseptics, antitussives, astringents, decongestants, demulcents and other classes and combinations of drugs [9-11].

Depending on the type of lozenge they may be prepared by

A) Molding : Pastilles

These are soft variety of lozenges contains medicament in gelatin or glycerogelatin base.

B) Compression of sugar based tablets : Troches

Advantages of lozenges over other dosage forms

- It can be given to those patients who have difficulty in swallowing.
- Easy to administer to geriatric and pediatric population.
- It extends the time of drug in the oral cavity to elicit a specific effect.
- Easy to prepare, with minimum amount of equipment and time.
- Do not require water intake form administration.
- Systemic absorption of drugs can be possible through buccal cavity.
- Taste of the drugs can be masked by sweeteners and flavors used in the formulation.
- Technique is non-invasive, as is the case with parenterals.
- It can Increase in bioavailability
- It can Reduced dosing frequency.
- It can reduce gastric irritation.
- It can improve onset of action.

- It can bypass of first pass metabolism.
- Improved patient compliance.

Disadvantages

- Some drugs may not be suitable with aldehyde candy bases eg; benzocaine.
- Children having above 6 years of age can use lozenges safely.
- The non-ubiquitous distribution of drug within saliva for local therapy.
- Possible draining of drug from oral cavity to stomach along with saliva.
- The lozenge dosage form is that it mistakenly could be used as candy by children.
- A hard candy lozenge is the high temperature required for their preparation.
- Hard lozenges become grainy.

Classification of lozenges

- According to the site of action

(a) Local effect Ex. Antiseptics, Decongestants.
(b) Systemic effect Ex. Vitamins, Nicotine.

- According to texture and composition-

(a) Chewy or caramel based medicated lozenges
(b) Compressed tablet lozenges
(c) Soft lozenges
(d) Hard candy lozenges

(a) Chewy or caramel based medicated lozenges [11,12]

These are the dosage form in which medicament is incorporated into a caramel base which is chewed instead of being dissolved in mouth. These lozenges are often highly fruit flavored and may have a slightly acidic taste to cover the acrid taste of the glycerin. These lozenges 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.. These gelatin-based pastilles were prepared by pouring the melt into molds or out onto a sheet of uniform thickness.

(b) Compressed tablet Lozenges [13]

When the active ingredient is heat sensitive, it may be prepared by compression. The granulation method is similar to that used for any compressed tablet. These tablets differ from conventional tablets in terms of

- Organoleptic property,
- Non disintegrating characteristics and
- Slower dissolution profiles.

The lozenge is made using heavy compression equipment to give a tablet that is harder than usual, as it is desirable for the troche to dissolve slowly in mouth. Commercially, the preparation of lozenges by tablet compression is less important.

(c) Soft Lozenges [2]

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.

Soft lozenges are similar to a historical form of medication that is making a comeback the "confection". Confections are defined as heavily saccharinated, 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.

(d) Hard Candy Lozenges [2]

Hard candy lozenges are mixtures of sugar and other carbohydrates in an amorphous (noncrystalline) or glassy state. They can also be regarded as solid syrups of sugars. The moisture content and weight of hard candy lozenge should be between, 0.5 to 1.5% and 1.5-4.5g respectively. These should undergo a slow and uniform dissolution or erosion over 5-10min., and should not disintegrate. The temperature requirements for their preparation is usually high hence heat labile materials cannot be incorporated in them. These pastilles were prepared by Heating and congealing method.

Methods

Candy Based Lozenges

(a) Heating and Congealing Technique [14]

Syrupy base was prepared in a beaker by dissolving the required amounts of sugar in water and kept for heating on a hot plate. Temperature was maintained at 105-110 °C till it became thick. The drug and other excipients (except plasticizer) were added manually and mixed thoroughly after 30 min with continue process of heating. The prepared mass was further heated for 45 min and then plasticizer was added into it. Then above syrupy base was poured into pre-cooled and prelubricated mold and the mold was kept aside for 10-15 min. Lozenges were removed from mold and were kept for air drying. In the case of batches without plasticizer, a step of plasticizer addition was omitted from procedure.

(b) Melting and Mold Technique [15,16]

PEG was melted on water bath and mixed with the other ingredients to form a homogeneous mixture. Subsequently, the mixture was poured into the desired shape & size stainless steel mold to forming a candy.

Compressed Tablet lozenges [2,15]

(a) Direct compression technique

Ingredients can be thoroughly mixed and directly compressed.

(b) Wet granulation technique

sucrose is pulverized by mechanical combinations to a fine powder then add binder solution and mass is formed and pass through # sieve no.16 granules formed & dried then add Lubricant, flavor prior to the compression.

Evaluation of Medicated Lozenges [17-20]

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 studies by pharmaceutical standard methods.

Diameter

The thickness and diameter of lozenges were determined using vernier callipers. Three lozenges from each batch were used and average values were calculated. The extent to which the diameter of the lozenges deviated from ± 5 % of the standard value.

Weight variation

The weight variation was conducted by weighing 20 lozenges individually and calculating the average weight and comparing the individual lozenges weight to the average value.

$$\textbf{Weight Variation} = \frac{Averageweight - Initialweight}{Averageweight}$$

Hardness

The hardness of the lozenges was determined by using Monsanto Hardness tester, where the force required to break the lozenges was noted. The hardness was measured in terms of (kg/cm^2).

Friability

The friability of the lozenges was determined using Roche Friabilator. Weighed lozenges were placed in the friabilator and operated for 4 min at 25 rpm. The tablets were then made free from dust and reweighed. The percentage friability was calculated.

Moisture content analysis

Moisture content in the final candy is determined by using Helium moisture balance apparatus. The sample was weighed and crushed in a mortar from this one gram of the sample was weighed and the moisture content is determined by the moisture balance apparatus.

Mouth dissolving time test

The time taken by the candy to dissolve completely was determined by the USP Disintegration apparatus, where hard boiled candy lozenges were placed in each tube of the apparatus and time taken for the lozenges to dissolve completely was noted by using phosphate buffer of pH 6.8 at 37 °C.

***In-vitro* drug dissolution studies**

The rate of dissolution possibly is related to the efficacy of the tablet lozenge. Dissolution study was carried out in 800 ml of phosphate buffer of pH 6.8 by USP II paddle method at 150 rpm. Samples were withdrawn at 5 min interval and replaced immediately with an equal volume of fresh buffer and were analyzed UV spectrophotometer.

Drug content

Appropriate number of lollipop are crushed and dissolved in an appropriate solvent and the absorbance of the solution is measured spectrophotometrically.

Stability studies

The stability studies were 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 IV) at 45°C and 75% relative humidity over a period of seven weeks. Sufficient number of optimized formulations were packed in amber coloured screw capped bottles and kept in incubator maintained at 37°C. Samples were taken at intervals of 15 days to estimate the drug content and to evaluate organoleptic properties.

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

Hard candies are hygroscopic and usually prone to absorption of atmospheric moisture. Considerations must include the hygroscopic nature of the candy base, storage conditions of the lozenges, length of time they are stored and the potential for drug interactions. These products should be stored in tight containers to prevent drying. This is especially true of the chewable lozenges that may dry out excessively and become difficult to chew. If a disposable mold with a cardboard sleeve is used, it is best to slip this unit into a properly labelled, sealable plastic bag.

Table 1. Marketed Products of Lozenges

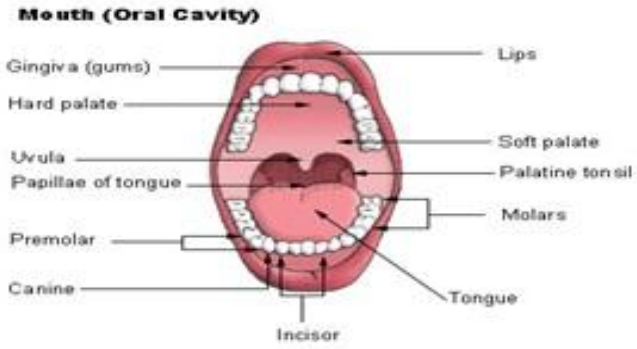
S.No	Product	Drug	Marketed /mfg. by	Category
1.	VICKS®	Menthol	Procter and Gamble Manufacturing company	Sore throat
2.	THERA ZINC®	Zinc (Gluconate)	Quantum health care	Common cold & flu
3.	NICORETTE®	Nicotine	Perrigo company	Smoking Cessation
4.	STREPSILS®	Amylmetacresol, dichlorobenzyl alcohol	Reckitt Benkiser healthcare Ltd.	Sore throat & blocked nose
5	CLOTRIMAZOLE LOZENGE®	Clotrimazole	Perrigo company	Oral thrush
6.	SUCRETS®	Dextromethorphan Hydrobromide	Insight Pharmaceuticals	Sore throat
7	CEPACOL®	Menthol,benzocaine	Combe Incorporated	Sore throat
8.	VIGROIDS®	Liquorices	Ernest Jackson and Company Ltd.	Expectorant
9.	CHLORASEPTIC®	Benzocaine	Prestige Brands lnc.	Relief of minor sore throat & mouth pain
10.	LOCKETS®	Eucalyptus and menthol	Wrigley Company	Nasal congestion & sore throat
11.	KOFLET-H®	Madhu	Himalaya Herbal Healthcare	Cough & quickly relieves throat irritation
12.	SUALIN®	Glycyrrhizaglabra	Hamdard (WAKF) Laboratories	Sore throat, cold & cough
13.	ANDOLEX-C®	Benzydamine	Inova pharmaceutical	Relief of minor sore throat
14.	FISHERMAN'S FRIEND	Menthol	Lofthouse chemical product Ltd.	Cough & sore throat relief.

Formulation of Lozenges

Table 2. Formulation of Lozenges [1]

S. No	Ingredients	Examples	Role
1.	Candy base Sugar Sugar free vehicles	Dextrose, sucrose, maltose, lactose. Mannitol, sorbitol, PEG 600 & 800.	These are the used as sweetening agent and impart the taste masking properties.
2.	Fillers	Di calcium phosphate, calcium sulfate, calcium carbonate, lactose, microcrystalline cellulose.	These are the used to Improve the flowability
3.	Lubricants	Magnesium stearate, calcium stearate, stearic acid and PEG, vegetable oils and fats.	These are the used to avoid sticking of candy to the teeth.
4.	Binders	Acacia, corn syrup, sugar syrup, polyvinylpyrrolidone, gelatin, tragacanth, and methylcellulose.	These are the used to hold the particles.
5.	Coloring agents	Water soluble and lakolene dyes, FD & C colors, orange color paste, red color cubes, etc.	These are the used to inhance appearance and organoleptic properties of dosage form.
6.	Flavorings agent	Menthol, eucalyptus oil, spearmint, cherry flavor, etc.	These are the used to give a taste.
7.	Whipping agent	Milk protein, egg albumin, gelatin, xanthan gum, starch, pectin, algin and carrageenan.	These are the used in toffee-based confection.
8.	Humectants	Glycerin, propylene glycol and sorbitol.	They improve chew mouthfeel properties.

Fig. 1. Anatomy of oral cavity



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