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A REVIEW STUDY ON- MEDICATED LOZENGES AS AN EFFECTIVE DOSAGE FORM

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ABSTRACT

In spite of several dosage forms available within the market place for effective action, the lozenges finds a special importance as they are the simplest dosage forms for formulating large dose of medicaments. The anatomy of mouth and cheek favours easy and effective systemic absorption of drug for better patient compliance and also especially for paediatrics and geriatrics patient because of their palatable taste imparted by the excipients. Lozenges are used for patients who cannot swallow solid oral dosage forms also as for medications designed to be released slowly to yield a continuing level of drug in the oral cavity. Lozenges are the flavoured medicated dosage forms intended to be administered and held in the mouth or pharynx containing one or more medicaments usually in the sweetened base. Lozenges are one of the very convenient and better innovative dosage form for oral confectionary products. Medicated lozenges enhances the retention time of the dosage form in mouth which increases bioavailability, reduces gastric irritation and bypasses first pass metabolism. Hence, Lozenges are an attractive, easily acceptable and most prominent dosage form for all the age group of population.

KEYWORDS: Lozenges, sugar- bases, crystallization, medicaments, temperature.

INTRODUCTION

The word "Lozenge" was derived from French word "Losenge", development of lozenges dates back to 20th century and is still in commercial production (S Maw., 1903). Lozenges are solid preparations that contain one or more medicaments, usually in a flavoured, sweetened base, and are intended to dissolve slowly in the mouth or pharynx.[1] Lozenges

with antimicrobial and local anaesthetics as active ingredient are mostly advised for patients with swallowing problems, gastrointestinal blockade, paediatrics and geriatrics as they can be sucked easily into the saliva, providing localized drug delivery to the mouth, tongue and throat etc.[2] It is a potentially useful for the administration of drugs either locally or systematically through the oral cavity because of the easy administration for the geriatric and paediatric patient and wide spread acceptance by patients. The development of new drug delivery systems for existing drug with an improved efficacy, avoid first pass hepatic metabolism, reduce gastric irritation, no need of water intake and increase bioavailability together with reduced dosing frequency.[3] Though the lozenges dissolution time is about 30 minutes, it also depends on the patient, as patient controls the rate of dissolution and absorption by sucking on lozenge until it dissolves. Sucking and the subsequent production of saliva may also lead to increased dilution of the drug.

Drug candidates which can be incorporated in lozenges belong to one of the following categories: antimicrobials and local anaesthetics for throat pain; aromatics, herbals, zinc salts, decongestants, anti-histamines and cough suppressants for cold, allergy, cough, congestion and nicotine like substances for smoking cessation.[4]

Definition

Lozenges are the more acceptable dosage form for all the different age population because of its palatable, flavoured taste with fast onset of action of drug. Lozenges are solid dosage form in which one or more medicaments are incorporated in a flavoured, coloured and sweetened base.

Advantages of Lozenges[5]

- Easy to administer to geriatric and pediatric patient.
- Systemic absorption of drugs can be possible through buccal cavity.
- It do not require water intake for administration.
- It can improve onset of action and enhance bioavailability.
- It can reduce dosing frequency.
- It can be prepared with minimal equipment.
- It can reduce gastric irritation.
- It improved patient compliance.
- Taste of the drugs can be masked by sweeteners and flavours used in the formulation.

Disadvantage of Lozenges[5, 6]

- It could be mistakenly used as candy by children.
- Children having above 6 years of age can use lozenges safely.
- Drugs having minimum bitter taste are suitable.
- Possible draining of drug from oral cavity to stomach along with saliva.
- High temperature required for their preparation.
- Hard lozenges become grainy.

Types of lozenges

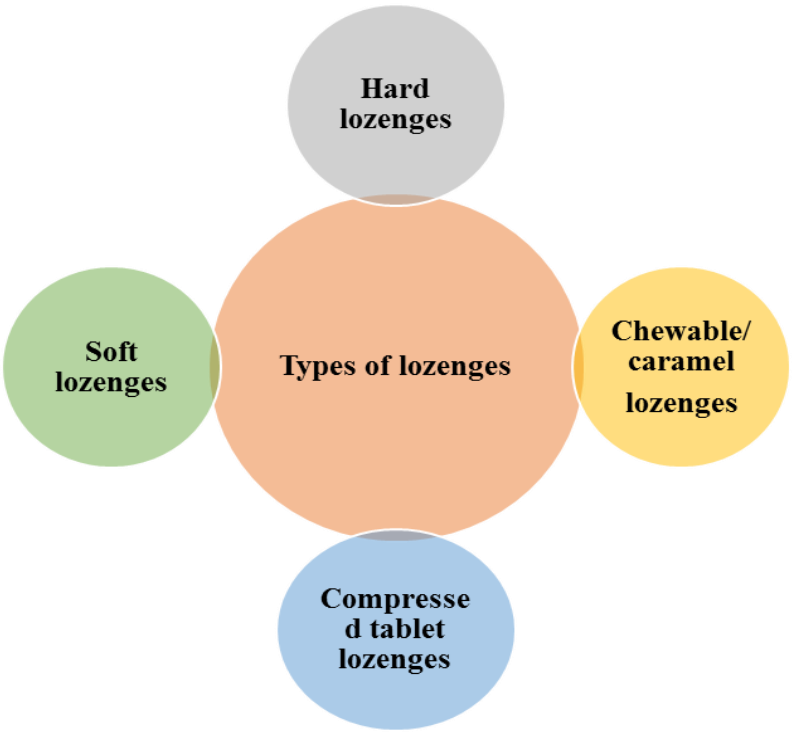

Figure 1: Types of lozenges.

(a) Hard candy lozenges

Hard candy lozenges are mixtures of sugar and other carbohydrates in an amorphous (non-crystalline) or glassy state. Lozenges are various-shaped, solid dosage forms usually containing a medicinal agent and a flavoring substance, intended to be dissolved slowly within the mouth 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.[7] Medicaments up to 2-4% can be incorporated in the hard candy lozenges. Sucrose, dextrose, maltose and lactose are added as sweeteners, citric, tartaric, fumaric and malic acid etc are added as acidulents to strengthening the candy base. Colours approved by

FD & C are added with shades like orange, red, green or yellow. Flavors used include menthol, eucalyptus oil, spearmint, and cherry flavor, mango, orange, etc.[9] 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. The temperatures required for the preparation is typically high hence heat sensitive ingredients cannot be incorporated into them.[10]

Manufacturing of Hard Candy Lozenges

Hard candy lozenges are prepared by heating and congealing technique. Sucrose is accurately weighed and is dissolved in one third amount of water by heating ablaze cookers until all sugar granules are dissolved. Liquid glucose is added when cooking temperature reaches 110° C and heating is continued till final temperature is 145° C to 160° C. The mixture is cooled to 135°C and colour is added. Further, cooling is carried out and mixed until temperature reaches 60°C. The flavour, drug and polymer are added and mixed for four to six minutes and poured in lubricated moulds. The prepared lozenges were wrapped in aluminium foil and store in air tight glass container or desiccator to prevent moisture uptake.[4]

Figure 2: Hard candy lozenges.

(b) Chewy or caramel based medicated lozenges

Chewy or caramel based medicated lozenges contains medicament incorporated into a caramel base which is chewed rather than being dissolved in mouth. These lozenges are made by using glycerinated gelatin suppository formula containing glycerin, gelatin, and water. The other ingredients incorporated are candy base, whipping agent, humectants, lubricants, flavour and the selected medicaments. [8] They are very highly flavoured 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.[7] The candy base consists of a mixture of sugar and syrup during a ratio of 50:50

to 75:25 sugar to syrup. The whipping agents are wont to incorporate air in toffee-based confections to get the specified degree of sentimental chew. These are exemplified by milk protein, egg albumin, gelatin, xanthan gum, starch, pectin, algin and carageenen. The humectants improve chew and mouth feel properties and include glycerine, propylene glycol and sorbitol. Lubricants are added to avoid sticking of candy to the teeth while chewing. It includes vegetable oils and fats. Medicaments up to 35-40% can be incorporated. Seeding crystal involves addition of fine granulated sugar at 3-10% to warm candy mass to hurry up the crystallization and permit the bottom to be formed into tablets in a much shorter time. Seeding crystals involves addition of fine granulated sugar at 3-10% to warm candy mass to hurry up the crystallization and permit the bottom to be formed into tablets in a much shorter time.[9]

Manufacturing of Chewy or Caramel Based Medicated Lozenges

The candy base is cooked at the temperature of 95-125^{o}c and transferred to planetary or sigma blade mixer. Mass is allowed to cool to 120^{o}c. This is followed by the addition of whipping agent below 105^{o}c. The medicaments are then added between 95-105^{o}c. Colour is dispersed in humectant and added to the above mass at a temperature above 90^{o}c. Seeding crystals and flavour are then added below 85^{o}c. Followed by lubricant addition and candies are then formed by rope forming and then packed using wrappers.[9]

Figure 3: Chewable lozenges.

(c) Compressed tablet lozenges

Compressed lozenges tablets are manufactured either be direct compression or wet granulation method. Thermolabile drugs can be made into a compressed lozenge tablets. The granulation method used for formulating lozenge tablets is as almost like to that used for normal compressed tablet. The compressed lozenge is harder enough so that it dissolves

slowly in the mouth. They have flat faced with sizes of 5/8-3/4 inch, weight 1.5-4 g, hardness 30-50 kg inch^2 and erosion time ranges between 5-10 min.[6] The ingredients for compressed tablet lozenges are tablet based or vehicles which are sugar such as dextrose, sucrose. Other vehicles are sugar free vehicles such as mannitol, sorbitol, polyethylene glycol (PEG) 6000 and 8000. Some commercially available sugar based vehicles include- Emdex, Nu-tab, Sweetrex, Mola-tab, Hony-tab, Sugar-tab. Other fillers include dicalcium phosphate, calcium sulphate, calcium carbonate, lactose and microcrystalline cellulose. Binders are also added to hold the particles of mass as discrete granules and include acacia, corn syrup, sugar syrup, gelatin, polyvinyl-pyrrolidone, tragacanth and methylcellulose. Lubricants are used to improve flow of ultimate troche mixture and include magnesium stearate, calcium stearate, stearic acid and PEG. The colours used include water soluble and lakolenedyes.[9]

Manufacturing of Compressed Tablet Lozenges

Manufacturing of compressed tablet lozenges can either be direct compression and wet granulation. In direct compression, ingredients are thoroughly mixed then compressed. In wet granulation, sugar content is pulverized by mechanical comminution to a fine powder (40-80 mesh size). Medicament is added and thoroughly blended. The blended mass is subjected to granulation with sugar or corn syrup and screened through 2-8 mesh screen. This is followed by drying and milling to 10-30 mesh size. Flavour and lubricant are then added before compression.[9]

Figure 4: Compressed tablet lozenges.

(d) Soft lozenges

They are either meant for chewing or for slow drug release in mouth. They will be made from PEG 1000 or 1450, chocolate or sugar-acacia base while some soft candy formulations can also contain acacia and silica gel. Acacia is employed to provide texture and smoothness and

silica gel is used as a suspending agent to avoid settling of materials to the bottom of the mould cavity during the cooling. The formulation requires heating process at about 50°c, hence is only suitable to heat resistant ingredients. These are mixtures of sugar and other carbohydrates in an amorphous (non-crystalline) or glassy state. They can also be regarded as solid syrups of sugars. The moisture content and weight of hard candy lozenge should be in between, 0.5 - 1.5% and 1.5-4.5 g respectively. These should undergo a slow and uniform dissolution or erosion over 5-10 min., and they should not disintegrate. The disadvantage of this method is that the temperature required for their preparation is high hence heat labile materials cannot be prepared.

Manufacturing of Soft Lozenges

On the account of the soft texture of those lozenges, they will be hand rolled then dig pieces or the nice and cozy mass are often poured into a plastic mould. Mould cavity should be overfilled if PEG is employed, as PEG's contract as they cool. This is often not required just in case of chocolate because it doesn't shrink. Phaechamud and Tuntarawongsa fabricated clotrimazole soft lozenges by molding method and evaluated the factors that affect the physical properties of lozenge. They found that increasing amounts of PEG 1500, xanthan gum or xylitol increased the hardness of the lozenge. And also disintegration time was found to be increased on increasing amount of actives and hardness.[9]

Figure 5: Soft lozenges.

Table 1: Material of Lozenges and their functions.[5,6,7,8]

SN	Ingredients	Examples	Role
1	Candy base Sugar Sugar free vehicles	Dextrose, sucrose, maltose, lactose. Mannitol, sorbitol, PEG 600 & 800.	These are use as a sweeting agent and impart the taste masking properties
2	Fillers	Dicalcium 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, Hpmc.	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, yellow, etc	These are the used to inhance appearance and organoleptic properties of dosage form.
6	Flavorings agent	Orange, mango, Cherry, Pineapple,vanilla, strawberry,etc.	These are the used to inhance appearance and organoleptic properties of dosage form.
7	Preservative	Methyl paraben, Propyl paraben	To protect from decomposition
8	Whipping agent	Milk protein, egg albumin, gelatin, xanthan gum, starch, pectin, algin and carrageenan.	These are the used in toffee-based confection.
9	Humectant	Glycerin, propylene glycol and sorbitol.	They improve chew mouthfeel properties.

1. Sugar: 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 importance as neutral sweeteners, their solubility properties, and their function as a ‘‘drier’’ to reduce the mass of the confection through crystallization.

2. Corn syrup: Corn syrup is used ini every type of confection to control sucrose and dextrose crystallization, which may lead to crumbling. Corn syrup in appropriate ratio with sucrose and dextrose allows the formation of an amorphous glass and develops a candy with the desirable appearance. The following physical properties of corn syrup are extremely important in the preparation of medicated candies: density, dextrose equivalent, hygroscopicity, sugar crystallization, viscosity, freezing point depression, and osmotic pressure. Sucrose crystallization is encountered in various food and pharmaceutical applications. In sucrose crystallization, diffusion of the sucrose from the bulk solution to crystal surface and integration of the sucrose molecule into the lattice structure are the typical rate-limiting steps. Many factors can affect the growth rate, including temperature, supersaturation, agitation, and impurities.[11]

3. Sugar bases: The sugar bases are associated with lozenge tablets are sucrose or compressible sugar, dextrose, mannitol, and sorbitol, which are available in special tableting grades from a variety of excipient manufacturers. Generally intended for direct compaction applications, they are utilized with the binders in wet-granulation systems. A non-nutritive sweetener is a synthetic or natural sugar substitute whose sweetness is higher than or comparable to sucrose. Examples of non-nutritive sweeteners like xylitol, mannitol, sorbitol, invert sugar etc.

4. Binders: Binders are generally intended for compressed tablet that are used to hold the particles of mass as discrete granules and include acacia, corn syrup, sugar syrup, gelatin, polyvinylpyrrolidone, tragacanth and methylcellulose, HPMC, etc.[12,13,14]

5. Lubricants: Lubricants are used to avoid sticking of candy to the teeth and improve flow of final troche mixture and include magnesium stearate, calcium stearate, stearic acid and PEG, etc.

6. Colorants: A color additive is any dye, pigment or substance which when added or applied to a food, drug or cosmetic, or to the human body, is capable (alone or through reactions with other substances) of imparting color. FDA is responsible for regulating all color additives to ensure that foods containing color additives are safe to eat contain only approved ingredients and are accurately labelled. [16] Colorants or coloring agents are mainly used to impart a distinctive appearance to the pharmaceutical dosage forms. Colorants are incorporated into medicated lozenges for product identification, good appearance and masking of physical degradation. 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 colours are excellent sources of information on current regulatory status of colorants.[22]

7. Acidulants: Acidulants are generally added to medicated lozenges to fortify and strengthen their flavour 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.

8. Preservatives: Since hard candy lozenges are hygroscopic, the water content may increase and bacterial growth may occur if they are not packaged properly. The prescence of water would dissolve some sucrose; the resulting highly concentrated sucrose solution is bacteriostatic in nature and would not support bacterial growth.

9. Flavours: Flavor esters are significant and versatile compounds, also known as important component of food, beverages, cosmetics, pharmaceuticals, chemicals and personal care products, like perfumes, body lotions, facecreams, shampoos, soaps, etc. Flavour refers to a mixed sensation of taste, touch, smell, sight and sound, all of which involve a combination of physiochemical and physiological actions that influence the perception of substances. Flavors are composed of different organic chemicals, such as hydrocarbons, alcohols, aldehydes, ketones, acids, esters or lactones. The low volatility and low molecular weight, usually lower than 400 Da, are responsible for a range of sensorial sensations attributed to the flavors. Flavor and aromatic esters are widely found in nature and confer pleasant organoleptic impact attributes, including fruity, floral, spicy, creamy or nutty aromas. These properties make possible a great variety of applications in the food sector in many beverages, candies, jellies, jams, wines and dairy products and also in the cosmetic industry, as fragrances in perfumes, de-odorants, creams and soaps and flavors in lip cosmetics.[15]

Table 2: Examples of flavours.[18]

SN	Taste	Flavours
1	Salty	Butterscotch, Maple, Nutty, Buttery
2	Bitter	Spicewild Cherry, Licorice, Chocolate Mint, Grapefruit, Coffee, Cherry, Peach,
3	Acrid	Raspberry, Orange, Lemon, Lime
4	Oily	Syrup
5	Sweet	Peppermint, Anise, Wintergreen
6	Acrid	Fruit, Berry, Vanilla
7	Metallic	Citrus berries, Mint, Grape, Marshmallow
8	Sour	Raspberry, fruits, berries, acacia

Evaluation of Medicated Lozenges[19,20,21]

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.

1 **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.

2 **Weight variation:-** Twenty lozenges were selected and weighed collectively and individually on an electronic balance. From the collective weight, average weight was calculated. Each lozenge weight was then compared with average weight to assure

whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

3 **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).

$$\%\text{weight variation} = \frac{\text{average weight - weight of each tablet}}{\text{average weight}} \times 100$$

4 **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.

% Friability = (Initial weight – Final weight) × 100 / Initial weight of lozenges

5 **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.

6 **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.

7 **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 250 ml of phosphate buffer of ph 6.8 by USP II paddle method at 50 rpm. Samples were withdrawn at 5 min interval and replaced immediately with an equal volume of fresh buffer and were analyzed UV spectrophotometer.

8 **Drug content:-**Appropriate number of lollipop are crushed and dissolved in an appropriate solvent and the absorbance of the solution is measured spectrophotometrically.

9 **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.

Packaging of Lozenges

Since the lozenges are hygroscopic in nature, a complex and multiple packaging is suitable. Packaging of lozenges is an important aspect to preserve its aroma, flavour, and avoid damages during shipping and transporting. Wax paper, aluminium foil, cellophane, polyvinyl chloride, seals against air, moisture, dust, germs. Lozenge is placed in air tight or moisture resistant glass container because they are protecting from microbes, contamination and unwanted human tampering. Blister pack is commonly used as unit dosage form.

Storage of lozenges

Lozenges should be stored faraway from heat and stored at temperature 15 to 20^{o}C. They should be preserving from extremes of humidity and at controlled humidity of 25 – 35 %. It's also based upon the storage requirement of the drug and therefore the base; either if room temperature or refrigerator is generally indicated.[17]

Applications of Lozenges

Lozenges are employed for the treatment of local as well as systemic disorders. Several drug candidates will be incorporate in lozenges or troches belong to one of the following categories: antimicrobials and local anaesthetics for throat pain; aromatics, herbals, zinc salts, decongestants, anti-histamines and cough suppressants for cold, allergy, cough, congestion and nicotine like substances for smoking cessation.

DISCUSSION

The formulation of lozenges is a simple and time saving process. It is a formulation which is more organoleptically accepted particularly by the paediatrics or geriatric patients. Medicated Lozenges will be ideal dosage forms for paediatric patients or geriatric patients. These will have additional advantages of patient compliance, convenience and comfortness for efficient treatment including low dose, immediate onset of action, reduced dosage regimen and economic. Lozenges are found better innovative dosage form and hold a crucial position in pharmaceutical field and can still remain as an equivalent in future.

CONCLUSION

Lozenges are medicated confections that are developed about 20th century ago and are still under commercial production. Most of the preparations are available over the counter products and are very economic dosage forms. They are designed for local also as systemic therapy. A wide range of actives can be incorporated within their structure. Lozenges provide easy administration, convenience to patient, large patient compliance and efficient treatment of low drug dosing, immediate onset of action, reduced dosage regimen and cost effectiveness. New drug design during this area always benefit for the patient, physician and drug industries. Lozenges will enjoy the foremost wanted position in pharmacy within the very near future.

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