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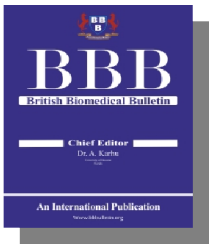

Review

A REVIEW ON LOZENGES

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A R T I C L E I N F O

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A B S T R A C T

Lozenges are solid, unit dosage form of medicament which are meant to be dissolved in mouth or pharynx. Development of lozenges dates back to 20th century and is still in commercial production. Most of the lozenge preparations are available as Over The Counter medications. Lozenge provide a palatable means of dosage form administration and enjoy its position in pharmaceutical market owing to its several advantages but it suffers form certain disadvantages too. The dosage form can be adopted for local as well as systemic therapy and a wide range of actives can be incorporated in them. Lozenges currently available in market are of four types: Caramel based soft lozenges, hard candy lozenges and compressed tablet lozenges. The present review covers more or less all aspects associated with lozenge. It includes various researches performed till date, formulation and evaluation parameters adopted for the dosage form. Furthermore, it throws light on the applications of lozenges.

Introduction

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.[1]

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 or 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.[2,3]

Lozenges are placed in oral cavity. Since the sublingual lozenges may be impractical due to their size, buccal lozenges are formulated and have been extensively used and are intended to be placed between the cheek and the gums. Though the lozenge 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. The consequence of this can be high variabilities in amounts of drug delivered each time the lozenge is administered. Sucking and the subsequent production of saliva may also lead to increased dilution of the drug and accidental swallowing.[4]

Depending on the type of lozenge, they may be prepared by molding or by compression. Molded lozenges are called pastilles while compressed lozenges are called troches.[3]

Lozenges should dissolve slowly in mouth and possess some degree of smoothness, with their shape being without corners.[5] Lozenges may be formulated with various shapes, like flat, circular, octagonal, biconvex or bacilli, meaning short rods or cylinders.[2]

Most of the lozenge formulations are available as Over the Counter (OTC) products where there is no need of prescription from a medical practitioner while some are prescribed by the medical practitioners.

Advantages

- Can be given to those patients who have difficulty in swallowing.[4]
- Easy to administer to geriatric and pediatric population.
- Has a pleasant taste.
- 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.[6]
- Do not require water intake for administration.
- Technique is non invasive, as is the case with parenterals.

Disadvantages

- It could be mistakenly taken as candy by children, hence should be kept out of the reach of children.[6]
- The non ubiquitous distribution of drug within saliva for local therapy.
- Possible draining of drug from oral cavity to stomach along with saliva.

Medicaments

Drug candidates which can be incorporated in lozenges, belong to one of the following categories:

- Antiseptics
- Local anesthetics
- Antibiotics
- Antihistaminics
- Antitussives
- Analgesics
- Decongestants
- Demulcents.[2]

Classification

- According to the site of action-

- Local effect. Ex. Antiseptics, Decongestants.
- Systemic effect. Ex. Vitamins, Nicotine.

- According to texture and composition-

- Chewy or caramel based medicated lozenges
- Compressed tablet lozenges
- Soft lozenges
- Hard candy lozenges

Chewy or Caramel Based Medicated Lozenges

These are the dosage form in which medicament is incorporated into a caramel base which is chewed instead of being dissolved in mouth.

Ingredients

- Candy Base- It consist of a mixture of sugar and corn syrup in a ratio of 50:50 to 75:25 sugar to corn syrup.
- Whipping agent- These are used to incorporate air in toffee-based confections to obtain the desired degree of soft chew. These are exemplified by milk protein, egg albumin, gelatin, xanthan gum, starch, pectin, algin and carageenen.
- Humectants- They improv chew and mouthfeel properties and include glycerin, propylene glycol and sorbitol.
- Lubricants- These are added to avoid sticking of candy to the teeth while chewing. It includes vegetable oils and fats.
- Medicaments- Medicaments up to 35-40% can be incorporated.
- Seeding crystals- It involves addition of fine powdered sugar at 3-10% to warm candy mass to speed up the crystallization and allow the base to be formed into tablets in a much shorter time.
- Flavors.

Manufacturing

The candy base is cooked at 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 ane then added between 95-105^{o}C. Color is dispersed in humectant and added to the above mass at a temperature above 90^{o}C. Seeding crystals and flavor are then added below 85^{o}C followed by lubricant addition above 80^{o}C. Candies are then formed by rope forming.[2]

Compressed Tablet Lozenges

If the active ingredient is heat labile, it may be made into lozenge preparation by compression. The granulation is prepared in a manner similar to that used for any compressed tablet.[2] The lozenge tablets differ from conventional tablets in terms of organolepticity, non-disintegrating characteristics and slower dissolution profiles.[3] 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. They are usually flat faced with sizes, weight, hardness, and erosion time ranging between, 5/8-3/4 inch, 1.5-4g, 30-50kg inch^{2} and 5-10min, respectively.[2]

Ingredients

- Tablet base or vehicle-
  - Sugar- Dextrose, sucrose.
  - Sugar-Free vehicles: Mannitol, sorbitol, polyethylene glycol (PEG) 6000 and 8000.
  - Other fillers- Di calcium phosphate, calcium sulfate, calcium carbonate, lactose, microcrystalline cellulose.

Some commercially available sugar based vehicles include- Emdex, Nu-tab, Sweetrex, Mola-tab, Hony-tab, Sugartab.

- Binders- These are used to hold the particles of mass as discrete granules and

include acacia, corn syrup, sugar syrup, gelatin, polyvinyl-pyrrolidone, tragacanth and methylcellulose.
- Lubricants- These are used to improve flow of final troche mixture and include magnesium stearate, calcium stearate, stearic acid and PEG.
- Colors- Water soluble and lakolene dyes.
- Flavors.

Manufacturing
- Direct compression- Ingredients can be throughly mixed and directly compressed.
- Wet granulation- In this sugar is pulverized by mechanical comminution to a fine powder (40-80mesh). Medicament is added and the mass is blended mass. The blended is subjected to granulation with sugar or corn syrup and screened through 2-8mesh screen. This is followed by drying and milling to 10-30mesh size. Flavor and lubricant are then added prior to the compression.[2]

Soft Lozenges

Soft lozenges are either meant for chewing or for slow dissolution in mouth. They can be made from PEG 1000 or 1450, chocolate or sugar-acacia base while some soft lozenge formulations can also contain acacia and silica gel. Acacia is used to provide texture and smoothness to the lozenge and silica gel is used as a suspending agent to avoid settling of materials to the bottom of the mold cavity during the cooling. The formulation requires heating process at about 50^{o}C hence is only suitable to heat resistant ingredients.[6,7]

Manufacturing

On the account of the soft texture of these lozenges, they can be hand rolled and then cut into pieces or the warm mass can be poured into a plastic mold. Mold cavity should be overfilled if PEG is used, as PEG's contract as they cool. This is not required in case of chocolate as it does not shrink.[7]

- 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 PEG1500, 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.[8]

Hard Candy Lozenges

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.[2,6]

Ingredients
- Bodying agent or base- This includes Corn syrup which is available on Baume basis. A 43^{o} Baume corn syrup is preferred in hard candy lozenges.
- Sweetening agent- It includes sucrose, dextrose, maltose, lactose.
- Acidulents- These are added to candy base to strengthen the flavor characteristics of the finished product. Commonly used acids are citric, tartaric, fumaric and malic acid.
- Colors- FD & C colors, orange color paste, red color cubes, etc.
- Flavors- It includes menthol, eucalyptus oil, spearmint, cherry flavor, etc.

- Medicaments- Medicaments upto 2-4% can be incorporated in the hard candy lozenges.
- Salvage- Salvage can be liquid or solid.[2]

Manufacturing

The candy base is cooked by dissolving desired quantity of sugar in one-third amount of water in a candy base cooker. This is continued till the temperature rises to 110°C. Corn syrup is added and cooked till the temperature reaches 145-156°C. The candy mass is removed from the cooker and transferred to a lubricated transfer container mounted onto a weight check scale where the weight of the mass is checked. This is followed by color addition in form of solutions, pastes or color cubes. The mass is then transferred to a water-jacketed stainless steel cooling table for mixing and the flavor, drug and ground salvage is added. The mass is either poured in mold or pulled into a ribbon while cooling and then cut to desired length. The obtained lozenges are packaged.[2,6]

- Cocaine voice tablet lozenges and pastilles were developed in late 1800's and were indicated in Extra Pharmacopoeia, 1888. They were used by singers and public speakers for the remedy of vocal huskiness and hoarseness.[9]
- Esimone *et al*., formulated and evaluated antimicrobial activity of herbal lozenge of garlic and ginger extract by molding method. The antimicrobial activity was evaluated against *Candida albicans, E.coli* and *Staphylococcus aureus* using Nystatin as standard. The formulation inhibited growth of laboratory strains of *C.albicans* but not *S.aureus* and *E.coli* and hence concluded that lozenges can be used in non-resistant oral thrush.[10]
- Greey *et al*., prepared penicillin agar pastilles. In order to prolong the retention time they tried gelatin, gelatin+agar and agar combinations with penicillin whose retention times were found to be 1hr, <1hr and 4-5hrs, respectively. This formulation has already been used in fuso-spirochaetal infection treatment and are being studied for hemolytic streptococcal infection treatment of throat.[11]
- A multicenter, randomized, double blind, single dose study was carried out by Wade *et al*., for assessing the efficacy of AMC/DCBA warm and cool lozenge for the relief of acute sore throat. Analgesic and sensorial benefits of AMC/DCBA warm and cool lozenge was compared against unflavored non-medicated placebo lozenge and significant analgesic, functional sensorial and emotional effects against the placebo were observed. Sore throat relief , difficulty in swallowing and throat numbness were observed, also emotional benefits included happiness, better feel and less frustration.[12]
- Shukla *et al.,* evaluated in vivo behaviour of controlled and pulsatile release pastilles for the treatment of asthma, COPD and for chrono therapeutic management of nocturnal asthma. They found that, enteric coating of pastilles delayed the in vivo drug release and can be used in nocturnal asthma.[13]

Center Filled Hard Candy Lozenges

These are the hard candy lozenges with soft or liquid centers into their main body.

Quality Control

General Checks- Candy Base Manufacturing

- As the candy base manufacture is commenced, a check on following parameters is performed: Corn syrup and sugar delivery gears; Temperature, steam pressure and cooking speed of precookers and temperature, steam pressure, cooking

speed and vaccum of candy base cookers.[2]

- Moisture analysis-
  - Gravimetric method- 1g sample is weighed and placed in vaccum oven at 60-70°C for 12-16hrs. Final weight is subtracted from initial and the difference in moisture content is calculated.
  - Karl Fisher titration- A sample calculated to contain 10-250mg water is taken in titration flask and titrated with Karl Fischer reagent.
  - Azeotropic distillation method- 10-12g candy is pulverized and placed in 500ml flask to which 150-200ml toluene is added. Flask is connected to a reflux condenser and is refluxed for 1-2hrs. Water collected gives the amount of water present in the sample.[2]
- Determination of sugar and corn syrup ratios-

This is performed by "Dextrose equivalent method: Lane Eynon Titration method".[2]

- Percentage reducing sugars-

Standard- 3g anhydrous dextrose is dissolved in 500ml water. The solution is boiled for 2min and 2 drops of methylene blue is added and titrated against 25ml of alkaline cupric tartrate solution (Fehling's solution) to a yellowish red end point.[2]

$$\frac{(3g) \times (\text{volume of standard dextrose solution Consumed by Fehling's solution})}{500}$$

= reducing sugar factor for 3g dextrose

Sample- 10g sample of candy base is dissolved in 250ml of water and titrated with 25 ml of Fehling's solution in the same manner as the standard.

$$\frac{\text{Reducing sugar factor} \times 100}{\text{Sample weight}/250 \times \text{Volume of sample solution consumed by Fehling's solution.}}$$

= Percent reducing sugar.

- Salvage solutions- Solid contents of salvage solutions is determined using a refractometer.[2]
- Forming checks- It involves a check on candy rope diameter.[2]
- Cooling checks- Visual inspection is performed in order to analyze any stress cracking due to rapid cooling, air bubble formation, surface cracking and black specks.[2]
- Physical and Chemical Testing-
  - Hardness- This is determined by Pfizer or Monsanto hardness tester.[14,15]
  - Diameter and thickness- This is determined by vernier calipers.
  - Drug excipient interaction studies- Determined by FTIR.[14]
  - Friability - Determined by Roche Friabilator operated at 25rpm for 4min.
  - Weight variation- 20 lozenges are weighed and average weight is determined. Individual weight is compared to the average weight.
  - In-vitro drug release- This is carried out in USP II paddle type dissolution apparatus.[15]
  - Drug content- Appropriate number of lozenges are crushed and dissolved in an appropriate solvent and the absorbance of the solution is measured spectrophotometrically.
- 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*
- *Staphyllococcus*
- *Salmonella.*[2]

- Stability Testing
- Stability testing of product- Lozenges are subjected to stability testing under following conditions-
  1-2months at 60°C
  3-6months at 45°C
  9-12months at 37°C
  36-60months at 25 and 4°C.[2]
- Stability testing of product in package- Lozenges in their final packs are subjected to following conditions for stability testing:
  25°C at 80%RH for 6-12months
  37°Cat 80%RH for 3 months
  25°C at 70%RH for 6-12 months.[2]

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.[3]

Storage

Lozenges should be stored away from heat and out of reach of children. They should be protected from extremes of humidity. Depending upon the storage requirements of both, the drug and the base, either room temperature or refrigerator temperature is usually indicated.[2]

Applications

Lozenges are employed for the treatment of local as well systemic disorders. A variety of drug candidates can be incorporated in them for the treatment of and relief from conditions of oral as well as throat infections such as oral thrush, sore throat, cough, gingivitis, pharyngitis, decongestant, etc. Moreover these also have been used to deliver the drug systemically for smoking cessation and pain relief.

Conclusion

Lozenges are medicated confections designed for local as well as systemic therapy. A wide range of actives can be incorporated within their structure. Most of the preparations are available as OTC products and are very economic dosage forms. These have been developed about 20th century ago and are still under commercial production. Lozenges enjoy an important position in pharmacy and will continue to remain at the same in future.

Authors' Contributions

Rachana Maheshwari has contributed to the acquirement of data and drafting of the manuscript.

Rehana Ansari has contributed in data acquisition. Dr. Vikas Jain has guided as well as reviewed and approved the version to be published. Dr. S.C. Mahajan and Mrs. Garvita Joshi have reviewed and approved the article for publication.

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Table 1. Types of center filled lozenges[2]

S.no.	Type of center filled lozenge	Composition	Fill Weight (%)	Shelf life (months)
1	Liquid fill	Fruit juice, sugar syrup, hydroalcoholic solutions or sorbitol solution.	10-20	6-9
2	Fruit center	Jams and jellies whose viscosity has been modified with corn syrup or liquid sucrose	20-25	12-15
3	Paste center	Granules and crystals formulated as paste	40	24
4	Fat center	Medicament or flavor being suspended or dissolved in hydrogenated vegetable oil	25-32	36-60

Table 1 provides a concise description on the types of center fills in hard candy lozenges.

Table 2. Applications of hard candy lozenges[16]

Active Ingredient	Applications
Amylmetacresol	Throat infection
Phenol	Throat infection
Benzocaine	Mouth and throat infection
Camphor	Sore throat relief
Hexyl resorcinol	Sore throat relief
Cetyl pyridinium chloride	Pharyngitis
Diphenhydramine	Cough suppressant
Menthol	Cough and sore throat relief Decongestant

Table 2 provides a list of some of the drugs which can be incorporated in lozenge and their area of applications.