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A REVIEW ON MEDICATED LOZENGES

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ABSTRACT

Lozenges are palatable solid unit dosage form administer in oral cavity. These are the flavoured medicated dosage forms proposed to be sucked and held in the mouth or pharynx containing one or more medicament usually in sweetened base. Lozenges show local effect at a particular site in oral cavity. A lozenge also shows systemic effect for which the drug undergoes circulation in bloodstream and exhibits its pharmacological action. Types of lozenges are compressed tablet lozenges, hard candy lozenges, chewy or caramel based lozenges, soft lozenges, center filled hard lozenges etc. These lozenges are formulated by using different ingredients like candy base, binders, lubricants, flavouring, colouring, whipping agent and humectants. Lozenges are evaluated by hardness, friability, diameter and thickness, weight variation, moisture content, drug content/ assay, etc. Drug – Excipients interaction are studied by FTIR. In- vivo study, In vitro study. Lozenges provide easy administration, convenience to patient, patient compliance, and efficient treatment of low drug dosing, immediate onset of action, reduced dosage regimen, and cost effectiveness.

KEYWORDS: Lozenges, local and systemic drug delivery, Excipients, prolonged release.

INTRODUCTION[1,2]

Lozenges are the flavoured medicated dosage forms proposed to be sucked and held in the mouth or pharynx containing one or more medicament usually in sweetened base. Lozenges are used to relieve oropharyngeal symptoms, which are normally caused local infection and also for systemic drug absorption. Medicated lozenges are designed to increase retention of dosage form in oral cavity which increases bioavailability, reduces gastric irritation and bypasses first pass metabolism. Lozenges are used for patients who are unable to swallow solid oral dosage form as well as for the medication designed to be released slowly to yield a

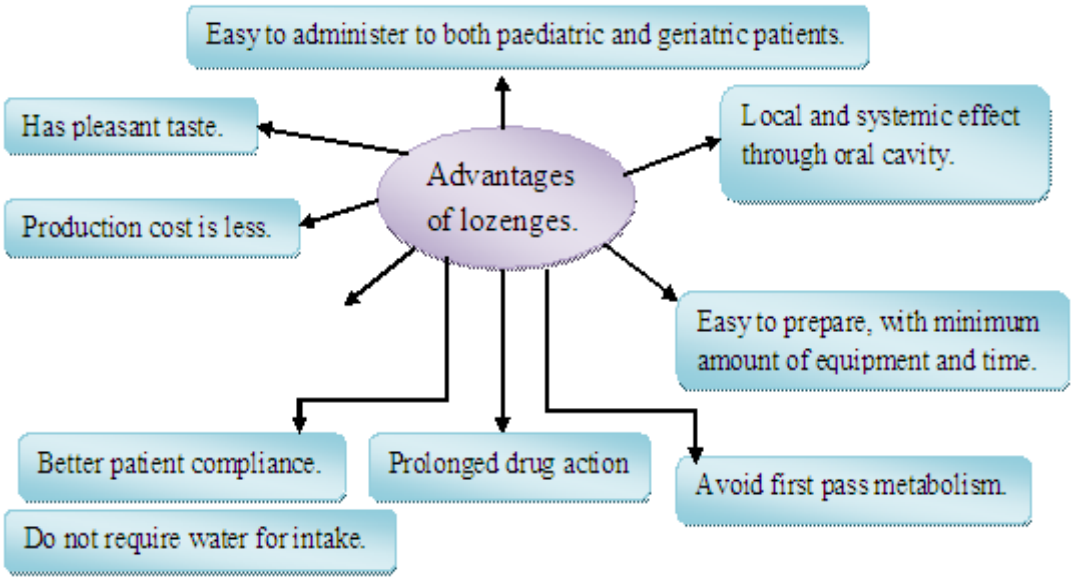
constant level of drug. Dissolution time of lozenges is about 30 minutes, it also depend on the patient, as patient controls the rate of dissolution and absorption by sucking on lozenges until it dissolves. Drug often incorporated into lozenges include analgesic, anti-tussives, aromatics, astringents, corticosteroids, decongestants, demulcent and many other supplement etc. Lozenges should dissolve slowly in mouth and possess some degree of smoothness, with their shape being without corners. Lozenges are formulated with various shapes, like flat, circular, octagonal, biconvex, rod shaped etc.

The consequence of this can be high variability's in amount of drug delivered each time the lozenge is administered. Sucking and the subsequent production of saliva may also lead to increased dilution of drug and accidental swallowing. Depending on the type of lozenges, they are prepared by moulding or by compression. Many ingredients are used for the preparation of lozenges are candy base, binders, lubricants, flavouring, colouring, whipping agents and humectants, etc.

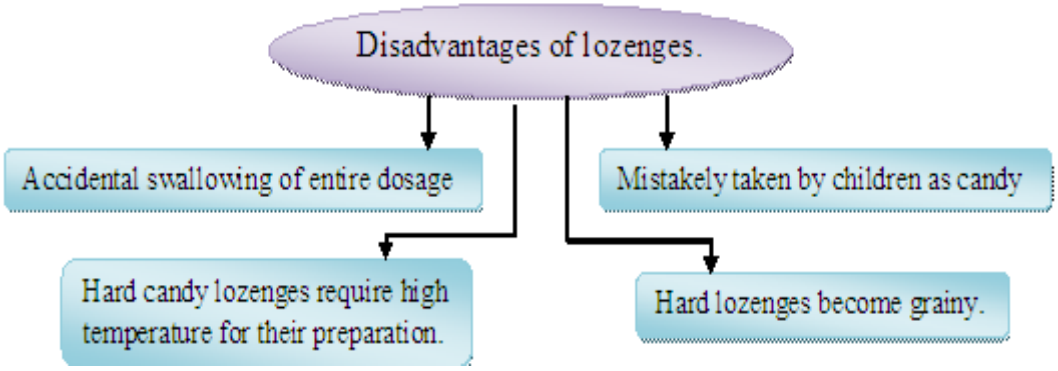
Most of the lozenges formulations are available as over the counter products where there is no need of prescription from a registered medical practitioner while some are prescribed by the medical practitioners.

Images of lozenges

Advantages of lozenges[3,4]



Disadvantages of lozenges[3,4]



Types of Lozenges[2,3,4]

Lozenges are classified into various methods classes based on various methods like

A) According to the site of action

a) Local effects E.g. antiseptics, decongestants.

b) Systemic effects E.g. Vitamins, Nicotine.

B) According to texture and composition

a) Chewy or caramel based medicated lozenges

b) Compressed tablet lozenges

c) Soft lozenges

d) Hard candy lozenges

Types of Lozenges And Their Manufacturing[4,5,6,7]

a) Chewy or caramel based medicated lozenges[4,5]

Chewy lozenges are popular with the paediatric population since they are "gummy type" lozenges. These are the dosage form in which medicament is incorporated into a caramel base which is chewed instead of being dissolved in mouth. They are prepared by using glycerinated gelatine suppository formula containing glycerine, gelatine and water. The other ingredients included are candy base, whipping agent, humectants, lubricants, flavour and the selected medicament.

Ingredients

- Candy base

It is made up of mixture of sugar and corn syrup in ratio of 50:50 to 75:25 sugars to corn syrup.

- Humectants

They are used to improve chew and mouth feel properties and include glycerine, propylene glycol and sorbitol.

- Whipping agents

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, gelatine, xanthan gum, starch, pectin, pectin, algin, and carageenee.

- Lubricant

Lubricant includes vegetable oils and fats to avoid the sticking of candy to the teeth while chewing.

- Medicament

35-40 % of medicament is incorporated in lozenges.

- Seeding crystals

Seeding crystals includes addition of fine powdered sugar at 3-10 % to warm candy mass to speed up the crystallisation and allow the base to form into tablets within a much shorter time.

- Flavours: - zinger, clove. Mint etc.

Manufacturing processes

The candy is cooked at 95- 125^{o}C and transferred to planetary/ sigma blade mixer.

↓

Mass is allow to cool to 120^{o}C. This is followed by addition of whipping agent below 105^{o}C.

↓

Then medicaments are added between 95- 105^{o}C.

↓

Colour is dispersed in humectants and added below 85 ^{o}C followed by lubricant addition above 80 ^{o}C.

Chewable or caramel lozenges are formed in the form of long rope of suitable thickness cut to a desired size and then packed by using wrappers. This process is called as rope forming.

b) Compressed tablet lozenges[6,7,8]

Methods used for manufacturing of compressed tablets lozenges are direct compression methods and wet granulation method. Thermolabile drugs are suitable for formulation of compressed tablet lozenges. Lozenges tablets are differ as compare to conventional tablet in terms of organolepticity, non-disintegrating characteristics and slower dissolution profile. Lozenges are formulated by using heavy compression equipment to give a tablet that is harder than usual. Lozenges are usually flat faced with size of 5/8- 3/4 inch, weight 1.5- 4 kg, hardness 30- 50 kg inch^{2} and erosion time ranges between 5- 10 min.

Ingredients

- Tablet base:-
- Sugar: - Dextrose, sucrose.
- Sugar free vehicles: - Sorbitol, mannitol, polyethylene glycol 6000 and 8000.
- Other fillers: - calcium carbonate, di calcium phosphate, calcium sulphate, microcrystalline cellulose.

- **Binders**

Binders help to hold the particles of mass as discrete granules. Binders used for manufacturing of compressed tablet lozenges are acacia, corn syrup, sugar syrup, gelatine, polyvinyl- pyrrolidone, tragacanth and methylcellulose etc.

- **Lubricants**

These are used to improve flow of final troche mixture and include magnesium stearate, calcium stearate, stearic acid and PEG.

- **Colours: -** Water soluble and lakolene dyes.
- **Flavours: -** zinger, clove etc.

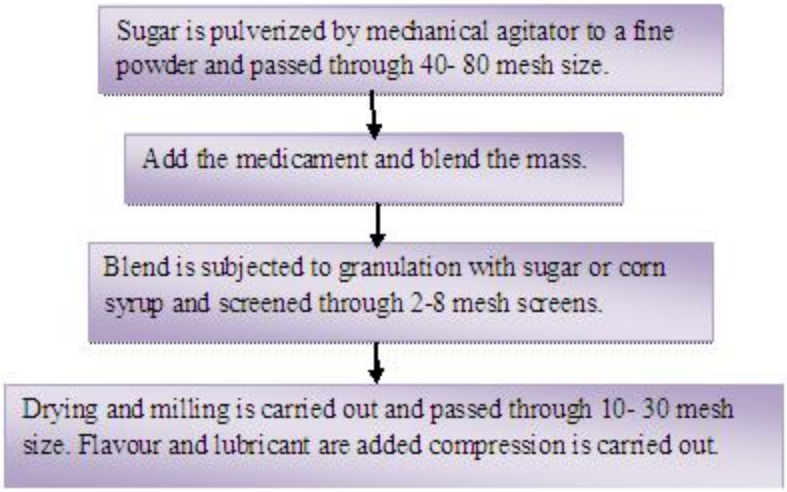
Manufacturing processes

Direct compression

In this method all the ingredients are thoroughly mixed and directly compressed in to lozenges tablets.

Wet granulation

Wet granulation method involves grinding of sugar in to by mechanical agitation and passed through sieve 40- 80 mesh size. Medicament is added to sugar mass and then mixed uniformly. Sufficient amount of sugar syrup or corn syrup is added to homogeneously mixed mass for the granulation and then passed through 2- 8 mesh size to obtain wet granules. These wet granules are dried and once again passed through 10- 30 mesh size. Suitable flavour and lubricant are the added before compression into required size of tablet lozenges.



c) Soft lozenges[9,10,11]

Polyethylene glycol 1000 or 1450, chocolate or sugar acacia base are used as base in the soft lozenges formulation and they gives soft texture to the lozenges. Some soft lozenges contain acacia and silica gel. Silica gel is used as suspending agent to avoid settling of materials to the bottom of the mould cavity during the cooling. They are formulated by using hand rolled

method to get desired size as well as thickness and cut in to pieces or the warm mass poured into a plastic mould to get soft lozenges. The formulation requires heating process at about 50^{o}C hence is only suitable to heat resistant ingredients.

Ingredients

- Base: - Polyethylene glycol 1000, Polyethylene glycol 1450, chocolate, sugar acacia base.
- Suspending agent: - silica gel. etc.

Manufacturing processes

Soft lozenges are manufactured by hand rolled and then cut in to pieces by maintaining desired size and thickness. Another method involves heating of all ingredients along with medicament at about 50^{o}C and poured into a plastic mould. Mould cavity should be overfilled if polyethylene glycol is used, as polyethylene glycol contracts as they cool. This is not required in case of chocolate as it does not shrink.

Soft lozenges containing Clotrimazole is made by moulding method in which the increasing amount of polyethylene glycol, xanthan gum or xylitol. This agent increases the hardness of the lozenges and hence the disintegration time care must be taken in the quantity of these agents.

d) Hard candy lozenges[12,13]

Hard candy lozenges are consisting of sucrose, other sugar/ carbohydrate in an amorphous or glassy state. They are made from aqueous syrup, the water which is initially present, evaporates as the syrup is boiled during the manufacturing processes for removing moisture. Moisture content should be between 0.5 to 1.5% and weight of hard candy lozenges lie between 1.5 – 4.5 g. They undergo slow and uniform dissolution over 5 to 10 min. High temperature is require for the preparation of hard lozenges so heat sensitive ingredients are not suitable for this formulation.

Ingredients

- Base

This includes corn syrup, which is available on baume basis. A 43^{o} basume corn syrup is preferred in hard candy lozenges. Sugar base, candy base are also used.

- Sweeteners

It involves sucrose, dextrose, maltose, lactose

- Acidulents

Citric acid, tartaric acid, fumaric acid, malic acid are used as acidulents. These are added to candy base to strengthen the flavour characteristics of the finished products

- Colours

Colours approved by FD and C like orange, red, green, yellow

- Flavour

Menthol, eucalyptus oil, spearmint, and cherry flavour. etc.

- Medicament

2-4% medicament can be incorporated in the hard candy lozenges.

Manufacturing processes

Hard candy lozenges manufactured by cooking processes by dissolving desired quantity of sugar to prepare the candy base and other carbohydrates in one third amount of water in the candy cooker at temperature about 110^{o}C. If corn syrup is used for the manufacturing of hard candy lozenges, the temperature should be kept in between 145- 156^{o}C. 2-4% medicaments are incorporated in hard candy lozenges. Other ingredients are added like sweetener, acidulents to strengthening the candy base, colours, flavouring agents. Colour is added in to it in the form of solution or paste and mixed uniformly. The weight of candy mass is checked by mounting the lubricated vessel containing candy mass. This mass is then transferred to a water- jacketed stainless steel cooling table for mixing of drug and flavour. The mixed mass is poured into mould to get desired and uniform lozenge as well as mass may also be pulled into a ribbon and after cooling it is cut into desired length to obtain lozenges which are packed as single unit wrappers.

e) Center filled hard lozenges

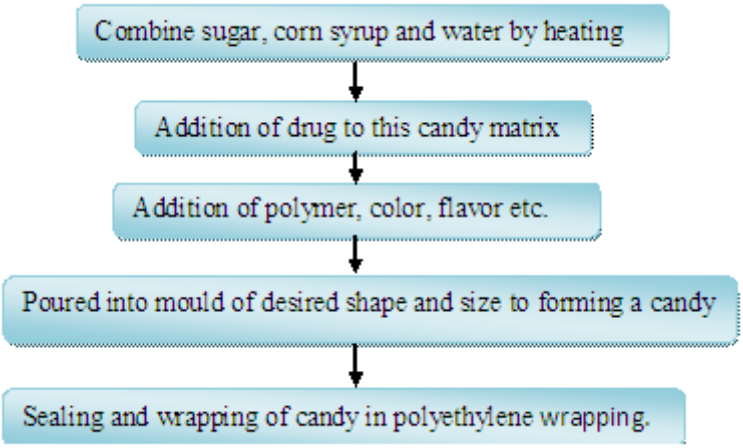
These lozenges are hard candy type with a soft or liquid filled center containing the active medicament. Different types center filled lozenges like liquid filled containing fruit juice, sugar syrup, sorbitol, solution or hydro alcoholic solution at about 10- 20% of fill weight. Some lozenges are fat filled center along with medicament and flavour. Medicaments are dissolved or suspended in hydrogenated fats with a fill weight of 25- 32%. Paste center filled lozenges, fruit center filled jellies and jams are also available in the market. Paste center filled lozenges consist of crystals and granules formulated as the paste with a 40% of fill weight. Fruit center filled jellies and jams where corn syrup or liquid sucrose had modified into a viscous gel form with a fill weight about 20- 25%.

Center filled hard lozenges are manufactured by forming a candy base or vehicle comprising sugar, corn syrup, and water, the candy base or the vehicle was heated to remove water there from to obtain a cooked candy base having a residual moisture content ranging from about 0.02% to about 5.0%. Then, subsequent cooling the candy base or vehicle to a soft state and forming the candy base in to a rope. The rope is wrapped around a filling pipe and the powder and semi-liquid center film was prepared containing, medicament in a stabilizing base including vegetable oil, and optionally sugar or gelatine, the semi- liquid or the powder center filler was dispensed into the center of the candy base or vehicle in a ratio of about 2 to 50% by weight of the medicament.

Formulation of Lozenges[4,8]

The lozenges are aimed to formulate into a stable dosage form and to provide a more promising means of administration of variety of drugs.

General method for preparation of medicated lozenges



Ingredients used in lozenges

Medicated lozenges are formulated by using various ingredients like sugar, corn syrup, acidulant, lubricants, binders, colorant, flavour, and the medicament etc.

Candy base

Sucrose

It is 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. Medicated lozenges are prepared by using Sucrose and sucrose products 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.

Invert sugar

Invert sugar is 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 humectants properties.

Corn syrup

It 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. Some physical properties of corn syrup are tremendously essential in the preparation of medicated candies: density, dextrose equivalent (DE), Hygroscopicity, sugar crystallization, viscosity, freezing point depression, and osmotic pressure.

Isomalt

It 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.

Colorants

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

Acidulants

These 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.

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. Some research has shown that excessive use of acidic lozenges could have the potential to enhance existing dental erosion, and that low pH (2.6–3.7) leads to dissolution of calcium and phosphorous from hydroxyapatite. Others have shown that excessive use of citric and tartaric acids may affect bioavailability of zinc in zinc lozenges. Another report indicated that the activity of cetyl pyridinium chloride in candy base lozenges is influenced by pH, with >5.5 being most desirable. Acceptable taste is necessary to ensure patient acceptability, and this can be the determining factor between commercial success and failure of an OTC product.

Flavours

These are used in medicated lozenges must be compatible with the drug and Excipients and able of withstanding the rigors of the manufacturing conditions. It consists 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 flavour–drug interaction is that of a primary amine drug (benzocaine, phenylpropanolamine) with aldehyde containing flavour components like cherry, banana, etc., resulting in the formation of a Schiff base, drug decomposition, and loss of efficacy. Adjustment of lozenge base pH to accentuate certain flavours (e.g., citrus) may also result in incompatibility with some medicaments (e.g., benzocaine).

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 colour, 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.

Sr. no.	Ingredients	Example
1	Candy base	
	a) Sugar	Sucrose, maltose, lactose, dextrose
	b) Sugar free vehicles	Polyethylene glycol 600 and 800, mannitol and sorbitol
	c) fillers	Lactose, calcium sulphate, calcium carbohydrate, dicalcium phosphate, microcrystalline cellulose
2	Binders	Acacia, corn syrup, sugar syrup, gelatine, polyvinyl pyrrolidone, tragacanth, methylcellulose.
3	Lubricants	Stearic acid, magnesium stearate, calcium stearate, polyethylene glycol, vegetable oil and fat
4	Flavouring agents	Menthol, eucalyptus oil, cherry flavouring, spearmint etc.
5	Colouring agents	Water soluble and lakolene dyes, food drug and cosmetic colour orange, colour paste and red colour cubes etc.
6	Whipping agents	Milk protein, egg albumin, gelatine, xanthan gum, starch, pectin, algin and carrageenan
7	Humectants	Glycerine, propylene glycol and sorbitol

Evaluation of Lozenges[1,4,8]

Physical and chemical testing

Hardness[8]

Hardness of the lozenges is determined by Pfizer or Monsanto hardness tester. The resistance of lozenges to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness.

Diameter and thickness[18]

A vernier calliper is the instrument used for the determination of diameter and thickness of the lozenges.

Friability[18]

Roche friabilator is used for the determination of friability of lozenges. Apparatus is rotated at 25 rpm for 4 min. Initial weights of lozenges are taken and they are placed in friabilator. After the revolution the lozenges were de-dusted and weighed again. The observed value not be more than 1%.

Friability is calculated by following formula

$\% \text{ friability} = (1 - Wt / W) \times 100$

Where, W= initial weight of lozenges

Wt= weight of lozenges after revolution.

Weight variation[8]

Twenty lozenges were randomly selected and individually weighed using an electronic balance. The average weight and standard deviation of 20 tablets was calculated or initial weight is compared with the calculated average weight.

Drug Excipients interaction studies[11]

Fourier transfer infrared analysis i.e. FTIR is used to study the Drug-Excipients interactions.

Disintegration test[11]

USP Disintegration apparatus is used to determine the disintegration time of lozenges. Disintegration time is noted in pH 6.8 phosphate buffer or artificial saliva at 37ºC.

In- vitro drug dissolution study[12,15]

Rate of drug absorption is determined by the rate of drug dissolution of the lozenges. Rate of dissolution and bioavailability is directly related to efficacy of lozenges. This study is carried out by using USP II Dissolution type apparatus (paddle type). Dissolution study was carried out in 900 ml of buffer pH 6.4 or use artificial saliva by USP II paddle method at 100 rpm. Samples were withdrawn at 5 min time interval and replaced immediately with an equal volume of fresh buffer or artificial saliva and were analyzed spectrophotometrically. Temperature $37^{o}C \pm 2^{o}C$ maintain between dissolution studies.

Drug content[12,15]

Drug content is done by taking an appropriate number of lozenges being crushed and dissolved in a suitable solvent and the absorbance of the solution is measured spectrophotometrically.

Moisture analysis[8]

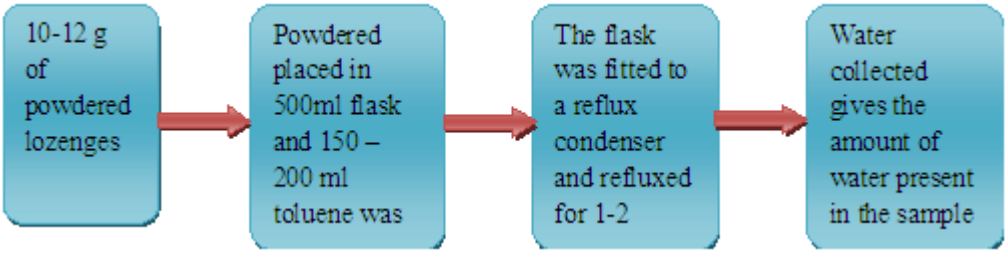
Moisture analysis can be done by using three methods like

Gravimetric analysis

Weigh accurately about 1g of sample and note the initial weight. It is then placed in a vacuum oven at 60-70 ^{o}C for 12- 16 hours. After specific period of time, once again weigh the sample and moisture content can be calculated by subtraction of initial weight from initial weight. Formula used for calculation moisture content is

Moisture content = Initial weight – Final weight

Azeotropic distillation method



Azeotropic distillation method for moisture analysis.

Karl fisher titration

A sample of the prepared lozenges is calculated to contain 10- 250 mg water is taken in titration flask and then it is titrated with Karl fisher reagent.

Stability studies[8,16]

The stability studies were performed to measure physical as well as the chemical stability of the drug, which may perhaps 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[16,17]

Lozenges 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[16,17]

Hard candies are hygroscopic and frequently 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 mould with a cardboard sleeve is used, it is best to slip this unit into a properly labelled, sealable plastic bag. Packaging should be proper and attractive.

Dispensing[16,17]

The patient should receive counselling about the purpose of a hard lozenge/troche which is to provide a slow, continual release of the drug over a prolonged period of time. Soft and chewable lozenges are to be taken only as directed and not considered as candy. They should be kept out of the reach.

Marketed Brand of Lozenges and It's Use

Sr. no.	Marketed brand	Drug	Use
1	Sore throat lozenges	Menthol and benzocain	Oral anaesthetics
2	Codral	Sour throat lozenges	Antibacterial anaesthetics.
3	Prospan	Hrdera helix extract	Chesty cough relief
4	ORAC 99k	Turmeric	Ayurvedic proprietary medicines
5	Equate	Nicotine	Stop smoking aid
6	Zinc lozenges	Vitamin C, ecbinacea	Diatary supplement
7	Difflamplus	Benzydiamine hydrochloride	Anaesthetics
8	Strepsils	2,4 Dichlorobezyl alcohol	Sore throat

Medication Given Through Lozenges

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

1. Antiseptics
2. Local anaesthetics
3. Antibiotics
4. Antihistaminic
5. Antitussives
6. Analgesics
7. Decongestant
8. Antifungal

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