Unexplored Potential of Medicated Candies And Lozenges as a Drug Delivery System

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Abstract

Candy formulation or Lozenges are types of solid dosage form which are considered as the divisions of tablets which slowly or gradually release the medicament in to the mouth over sustained period of time. They have prominent action in the local infections such as in the pharynx or mouth cavity infection but quite a few of lozenges are now being used systemically. Lozenges formulations are usually preferred for prominent candidate drug for first pass effect. Lozenges consist of different types of formulation such as chewable lozenges, hard lozenges, soft lozenges which have proven to be helpful for all categories of patients showing special compliance to the pediatric patients. Hard candy comprises uniform mixture of sugar (carbohydrates)especially sucrose in amorphous state. The present review covers more or less all aspects associated with lozenges and also deals with various applied concepts of them in treatment. Lozenges provide a palatable and compliable means of dosage form and have stamped its authority in pharmaceutical market owing to its several advantages, but it suffers from 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.

KEYWORD- LOZENGES; MEDICATED CANDY; ORAL DRUG DELIVERY; SWEETENERS; THROAT INFECTION

Introduction

James Lofthouse an Englishman formulated a strong bronchial mixture in 1865 which contained menthol, eucalyptus oil, capsicum and liquorice formulated as a mold by placing onto sugar cubes and forming a hard bound formulation, but this spilled into the sea, so he reformulated this mixture into a solid form – with the same ingredients mixed in a sugar and gum base compressed or molded with water, which is further rolled, cut and shaped. The USP presently approves Nystatin Lozenges and Cetylpyridinium Chloride Lozenges. The quantity of OTC marketed lozenges has risen upto almost five dozen in the current marketing scenario. [1]

Lozenges release the drug in the buccal cavity at a salivary fluid environment and are used for local action and medication in the mouth or throat remedies such as local anesthesia, antiseptic and antibiotic action of drugs as well as for systemic effectif the drug ensures optimumabsorption through the buccal lining or is swallowed. Lozenges resemble the conventional tablet but they don't contain the disintegrant. They also contain other excipients such as color, filler and binder based on the type of lozenges. [2]

Lozenges are solid dosage form mainly in a flavored, sweetened base, that contains one or more medicaments which dissolve or disintegrate slowly in the mouth. Lozenges can be prepared by hot

molding with gelatin and/or fused sucrose and sorbitol base or by compression of sugar-based tablets, molded lozenges (known as pastilles) and compressed lozenges called troches. They are intended to be allowed to dissolve on the back surface of the tongue to provide maximal local drug delivery [3]

Probiotics have also evoked new researches in the last years in the development of lozenge which indicates that former provides important benefits to the oral health, preventing caries helping periodontal and halitosis disease treatment and reducing the amount of bacteria related to oral pathology.[4]Lactobacillus bravis CD2 lozenges reduce radiation and chemotherapy-induced mucositis in patients with head and neck cancer as found in a randomized double-blind placebo-controlled study[5]

Various types of formulations of lozenges are available in market to treat or prevent local infection of throat and other systemic infection such as zinc lozenges to the treatment of common cold[6], antimalarial lozenges of Artisunate for pediatric[7] nicotine based candies for the cessation of smoking [8].

History And Origination of Candy Dosage Form-

In 1865, a private limited company named Lofthouse of Fleetwood was set up to commercialize the product. Further expansion of the company in terms of staff occurred in 1980s and 1990s.

Currently, the company produces 1.2 million packets of these preparations a day, using machines having an ability to produce 400,000 lozenges an hour; however these results were better than hand production technique where output rarely exceeded 6000 lozenges a day. It is reported that Margaret Thatcher(Former British Prime Minister) used lozenges to ease her throat after public speaking and Placido Domingo(a popular Spanish tenor, conductor and arts administrator) to ease his throat after singing and speech.[9]

Main advantage of candies dosage form includes its administration without water which further ensures improved patient compliance because of its pleasant and acceptable sweet taste and major disadvantage includes its high calorie content because of its “sugary base” which increases the risk of increased glycemic index in diabetic patient as well non-consumable by obese population. The word “Lozenge” finds its origination from a French word “Losengey” which stands for a diamond, which consist of four equal sides. Lozenges are the flavored medicated dosage forms intended to be sucked and kept in mouth for prolonged periods such that the medicament elutes easily in the saliva thereby providing local prolonged effects.

Lozenges are basically used to lessen oro-pharyngeal symptoms, which are usually caused by localized infections and also can be put to systemic effect provided the drug provides optimum absorption rate through the buccal linings or when it is swallowed. This drug delivery system therefore can be used for absorption by both pathways i.e. local and systemic. Drug absorbed directly via the buccal membrane has an advantage over other mechanisms of metabolism in the gastrointestinal tract as the occurrence of first pass effect of the liver is overcome by it. As a result reduced dose can be incorporated compared to other oral drug delivery systems. A similar pathway has also been adopted by medicated chewing gum for drug delivery. [10]

Advantages-

Following are some of the advantages of lozenges:

a. Lozenges have a definite size and shape so can be easily given to both geriatric and pediatric population. Most attractive for the children due to their various shape such as toys, animals, heart etc.

b. Sugar free lozenges can also be safely used for diabetic patient.

c. Bitter drug or drug having unpleasant smell or odour can be given with taste and odour masking agent.

d. Easily prepared so have time consuming and require minimum equipment.

e. By-pass first pass metabolism, reduce gastric irritation and increase bioavailability.

f. Do not require water for administration and have non-invasiveness.

g. Can be given for patient having difficulty in swallowing.

Disadvantages-

The disadvantages of lozenges are summarized as:

a. The most major disadvantage includes its resemblance to sweet sugar candies fantasized by children, hence should be kept out of the reach of children.

b. High temperature required for the preparation of hard candy lozenges.

c. Hard lozenges become grainy.

Categories of Drugs Administered In Lozenges-

Various type of drug can be incorporated into lozenges which may possess local or systemic action such as antiseptics, antibiotics, local anesthetics, antihistamines, demulcents, Anti-tussive, decongestants, analgesics.

Classification of Lozenges-

Lozenges may also be classified by various types such as shape, size, texture, site of action such as local acting or systemic acting depend on their uses.

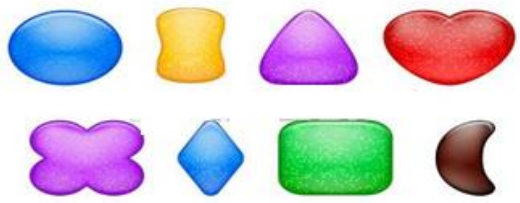

Figure.1 : Various shapes and sizes of candies

a. According to the site of action-

According to the site of action lozenges may be:

a. Local acting eg. Antiseptic

b. Systemic acting eg. Antihistaminic drugs

Table 1: Types of lozenges

S. No	Type of center filled lozenges	Composition	Fill weight (%)
1.	Liquid-filled	Fruit juice, sugar syrup, hydro alcoholic solutions or Sorbitol solution.	10-20
2	Fruit center	Jams and jellies whose viscosity has been modified with corn syrup or liquid sucrose.	20-25
3.	Paste center	Granules and crystals formulated as paste.	40
4.	Fat center	Medicament or flavor being suspended or dissolved in hydrogenated vegetable oil.	25-32

b. According to the Composition-

i] Chewable lozenges-

These types of lozenges don't dissolve in to the mouth but they are chewed because of their gummy nature . Made up of various types of gum like, carrageenan, xanthan gum, starch, pectin and algin, mainly they are the combination of gelatin, glycerin and water which are formulated by heating all the component . They contain high concentration of flavoring agent for covering the acrid taste of glycerin. [11]

ii] Hard lozenges-

Hard lozenges are the non-crystalline amorphous solid mixture of sugar and carbohydrate (also known as solid syrup of sugar). Advantage of these includes avoidance of first pass metabolism because of which the drug dissolve into the buccal cavity or in the gut after swallowing. They contain moisture about 0.5 - 1.5% and dissolve or erode in about 10 minutes.

One disadvantage of hard lozenges that is requires high temperature for the formulation. It is mainly used for the throat infection, demulcent and soothing action of throat or any infection of the mouth. [12]

iii] Soft Lozenges-

Soft lozenges are widely used because of their nature, they can be given to patient such as pediatric or geriatric. They release the drug slowly for a specific period of time and may be acacia, PEG or silica based formulation. Silica act as suspending agent in this formulation which prevent the settling of material at bottom during cooling of formulated material. They can be formulated by simple cutting of roll by hand or by pouring the hot melted material in to a mold and further cooling it for forming the shape of sachets.[2]

Special Types of Lozenges-

A) Zinc Lozenges-

Eby et al. in 1984 used 23 mg zinc gluconate throat lozenges which reduced the time period of common cold by almost 7 days.[13]

B) Zinc Effervescent Tablets-

Douglas et al.in 1987 RCT mentioned the use of additive food acids in their ‘‘effervescent” zinc acetate lozenges used to treat natural colds in 63 subjects in Adelaide, South Australia.[14]

C) Dispersible lozenges-

In 1987, Al-Nakib et al.in British Medical Research Council Common cold Unit (CCU) in Salisbury, England formulated lozenges containing 23 mg zinc (16.56 mg iZn) used 9 times per day to treat HRV-2 rhinovirus-induced colds in 12 patients. Lozenges were seen to dissolve in the mouth in a time period of 20 min.[15]

D) ZG lozenges :

Weisman et al. in 1990 studied ZG lozenges given 10 times per day in a group of 130 subjects in Copenhagen, Denmark to treat natural colds. He found no statistically significant effect of the lozenges on cold duration. [16]

E) Zinc acetate (ZA) lozenges:

Petrus et al.in 1998, using zinc acetate (ZA) lozenges, found significant reductions in mean duration of common cold specially in children.[17]

F) Dextromethorphan entrapped Polymer based sustained release candies-

Sustained release matrix tablets of Dextromethorphan hydrobromide were prepared by wet granulation using hydroxyl propyl methyl cellulose as the hydrophilic rate controlling polymer. On the other hand DXM resinate received attention for the same purpose using Amberlite® IRP69 and DowexR50W.

Complexes of ion-exchange resin and Dextromethorphan were prepared using different particle sizes of the resins, where aqueous colloidal dispersions of ethyl cellulose and polyvinyl acetate (Kollicoat® SR30D) were used for fluid-bed coating. The ion-exchange capacity, the degree of cross-linking, as well as resin particle size affect DXM release. [18]

G) Polyherbal extract based linkus Lozenges for symptomatic relief of cough –

Rehman et al. in 2017 formulated polyherbal extract based linkus Lozenges for symptomatic relief of cough.[19]

H) Antipyretic and analgesic-

Pattnayak et al.(2012) formulated paracetamol lozenges to provide slow release medicament for the management of fever and pain. [20]

I) Montelukast sodium lozenges-

Rao et al. (2013) formulated as a oral retentive lozenge for the treatment of asthma in pediatric

patients.[21]

J) Infant anti-viral Lozenges-

Dhumal et al.,(2016) formulated infant ketoconazole candy for relieving oral thrush of hardness 12-13 kg/cm.[22]

K) Sulfate hard candy lozenges

Rathananad et al. (2011) investigated the replacability of Isomalt and liquid glucose as sugar substitutein the operation involving the formulation of Salbutamol sulfate hard candy lozenges. [23]

L) Nicotine hard candy lozenges

P. Renuka et al. (2011) developed and in-vitro evaluated nicotine hard candy lozenges for smoking cessation.[3]

Table 2: Candies used in different disease or disorder

Sr. no.	Disease	Candies	Active component	Characteristic& Use
1	Throat Cancer	Lactobacillus brevis CD2	Lactobacillus brevis	Throat and head cancer
2	Dry cough	Dextromethorphan	Dextromethorphan	Dry cough
3	Stress and upset	Zonic	Nicotine	can help if you really want to quit smoking.
4	Oral ulcer	Lactobacilli	Lactobacillus acidophilus	Antiulcer having anti-inflammatory activity
5	Mouth and throat infection	Dequadin	Dequalinium	Antiseptic effect against range of bacteria
6	Candida and oral thrush	Fungilin	Amphotericin B	Antifungal effect used to treat oral thrush and candida
7	Cancer	Probiotic lozenges	*E. faecium* CRL 183	The probiotic lozenge produced showed anticariogenic potential.

Component of Lozenges

There are various types of components required for making a good lozenge in which base has most important role for developing the lozenges. Lozenges contained various component like Sweeteners,fillers, flavouring agents, preservatives, colouring agents, API, Suspending agents. However the choice of each one of these depends upon the type of finished product desired by the manufacturer.

[A] Sweeteners-

Sweeteners may be called as the “body of lozenges” because apart from giving a desirable characteristic sweet taste to the formulation, they also perform the job of slowly releasing the drug and masking the unpalatable taste on long term usage so selection of the Sweetenersare based on their compatibility with the drug, their sweetening value, adverse effect on the formulation is most important. [24]

Table 3: Ingredients used in formulation of lozenges

Ingredients	**Example**
Candy Base 1. Sugar 2. Sugar free vehicles 3. Fillers	Sucrose, maltose, lactose, dextrose Polyethylene glycol (PEG) 600 and 800, Mannitol, Sorbitol, calcium sulphate, lactose. Microcrystalline cellulose etc.
Binders	Acacia, corn syrup, sugar syrup gelatin, Polyvinyl Pyrollidone, Tragacanth etc.
Lubricants	Stearic acid, Magnesium stearate, Polyethylene glycol, vegetable oil and Fats etc.
Flavouring agents	Menthol, Ecalyptus oil, Cherry flavor, Spearmint etc.
Colouring agents	Water soluble and Lakolene dyes, orange colour paste and red colour tubes etc.
Whipping agents	Milk protein (casein), Egg albumin, gelatin, Xanthan gum, starch, pectin, carageenan
Humectants	Glycerin, Polyethylene glycol, Sorbitol

The Sweeteners came in Food Regulations in 1983, however at that instance only one intense sweetener which was saccharin, was approved for use in the UK. Cyclamate, another sweetener was subjected to prohibition since 1970 due to safety concerns over its usage. However in 1983 three new intense sweeteners i.e. aspartame, acesulfame K and thaumatin were approved and also added to saccharin for use in food products. Between the time of 1982 to 1993 this has resulted in an increase in the total market of intense sweeteners in the UK by about 400 per cent. [24]

Table 4: List of Natural and artificial Sweetener used in preparation of Candy

S.No	Name of Sweetener	Type	Brand name	Discovery& source	Use
1	Acesulfame K,	Artificial	Sunett and sweet	Accidentally discovered by a chemist in 1967. It is 180-200 times sweeter than sucrose	widely used in foods, beverages and pharmaceutical products
2	Aspartame,	Artificial	Neutra sweet ,amino sweet	First synthesized by a chemist in the course of producing antiulcer drug candidates in 1965.	juices, laxatives, chewable vitamins supplements, milk drinks, pharmaceutical drugs and supplements,
3	Cyclamate	Artificial	Sugar twin	It was discovered in 1937 by graduate student working in the lab on the synthesis of anti-fever medication.	It is often combined with other artificial sweeteners, especially saccharin
4	Maltitol	Artificial	Maltisorb, maltiweet	Made from maltose has 75-90% of the sweetness of sucrose	Used to replace table sugar because it has fewer calories, does not promote tooth decay, and has a somewhat lesser effect on blood glucose,
5	Stevia	Natural	Turevia , purevia	The common name of stevia rebaudiana	It is used by native healers to treat diabetes
6	Glycyrrhizin	Natural	Ammonium glycyrrhizinate	Obtained from glycyrrhiza glabra	It is used as natural sweetener in pharma product having adaptogenic effect.

[B] Flavouring agents-

Flavouring agentsare used in very less amounts for imparting the acceptance of the lozenges to patient same as the colouring agent. They may be artificial or natural.

[C] Colouring agents-

They are added in little amounts for attracting human for consumption of lozenges and masking the fade colour of lozenges which may arise due to the drug, colouring agents or other colored excipients or colour gained during the processing of lozenges usually under effects of heat and temperature storage conditions**.** Water soluble coloursare mainly preferred.

[D] Preservatives-

Preservative are added in the formulation to protect the lozenges from microbial contamination, environmental issue, and other condition. Different categories of preservatives are used which are required mostly in the case when sugar component are added in large proportion or when contain peptide or protein along with main additives which are candidates of rapid distortion under process conditions.

Table No. 5: Preservatives used in lozenges

S. No	Preservatives	Indication
1	Modified soybean phospholipid	As a good natural food emulsifier, can be used in biscuits, cakes, margarine food, candy and ice cream
2	Potassium nitrate	Natural source of nitrogen
3	Nisin	A polycyclic antibacterial peptide with 34-amino acid residues used as a food preservative
4	Potassium sorbate	Effective in a variety of applications including food, wine, and personal care products.
5	Capryl monoglyceride	In sanitarian foods and other foods, such as sweetened bean paste, cake and moon-cake.

[E] Bulking agents-

Bulking agents used when the amount of active constituent are less in quantity. They are mostly used in the direct compression process of lozenge formulation**.**

Table No. 6:Patent on different Lozenge Formulations and their processing requirements

S. No	Name of patentee	Patent No.	Patent date	Patent based on	Table Reference
1	F. E. Zaiss	US1,400,127	Dec 13 1921	Machine for making spiral based candy	1
2	Mayes et al.	US 7,552,707B2	Jul13 -2010	Bag cag having bag candy	2
3	R. C wallface	US 3232244	Feb 1 -1996	Cotton candy machine	3
4	G. H caller	US 2956520	OCT 18-1960	Candy forming machine	4
5	Charles D.	US2011/0027 434	Feb 3-2011	Candy popcorn cooker and mixer and their associated use	5
6	S. Dempesy	US1414553	May2-1992	Chocolate candy cooler	6

7	Moore et al	US5626896	May 6 – 1997	Method for making liquid jelly center candy	7
8	A. M. Stryker	USRE16857	Aug 5 – 1923	Candy containing and displaying device	8
9	J. Jeeper	US781527	Jan 31 -1905	Candy holder	9
10	G. Sorensen	US1688668	Oct 4 -1926	Candy cutting machine	10
11	Newman	US2006/0094 734	May 4-2006	Composition and method including alert.	11
12	Harry missel	US3114642	Apr 20-1962	Hard candy and process for making same	12

Mechanism of Drug Release In Case of Candy

Drug releasesout from the lozenges for a specific period of time then resulting in mixing of drug withthat of saliva. That causes the release of drug from the lozenge and absorption of drug occurs at this site which is richly supplied with blood flow futher absorbed from the oral mucosa(for local effects) or the content can be swallowed reaching the stomach for gastro-intestinal absorption(for systemic effects). Thus there are mainly two possible pathways by which lozenges drug medicament can be absorbed or reached in to systemic circulation

a. Firstly absorption of drug through the buccal membrane which prevent the drug from getting metabolised in the gastrointestinal tract and first pass metabolism of the liver.
b. Second method ensures absorbtion for systemic effect and is usually achieved by the lateral parts of GIT. [25]

Methods of Formulation of Lozenges

Medicated candy is prepared by using heating and congealing method by the following steps:

(a). Firstly Syrup base is prepared by dissolving the required amount of sugarin to water and heating at 110^{o}C for about 90 min.

(b). Then cooling to obtain the plastic mass.

(c). Then Addition of drug, polymer, color, flavor agents with the proper mixing.

(d). After the complete mixing, the resultant mixture is poured into molds for desired shape and allowed to cool at room temperature.

(e). Then wrapping the lozenges by polyethylene wraps. [26]

There are different types of method for formulation of lozenges as according to their nature such as soft lozenges, hard lozenges and chewable lozenges..

Preparation of compressed tablet lozenges

(a)Direct compression- Ingredients and excipients are mixed uniformly then directly compressed to form

a hard candy mass.[2]

(b)Wet granulation- This method includes the pulverization of sugar by mechanical comminution and its conversion to a fine powder (40-80mesh). The medicament is then added and then the mass is blended. Thispre-blended massis then taken for granulation with sugar or corn syrup and screened through 2-8mesh screen. Drying and milling operations are then done to 10-30mesh size. Flavors and lubricants are then added after compression. Wet granulation process further involves three sub-methods for lozenge formulation:-

(i) Preparation of compressed tablet lozenges by the method of ordered mixing -Ordered mixture is prepared by adding the sieved (80#) drug in small parts to the weighed amount of Iso-malt and mixed thoroughly for 30 min. Weighed amounts of other excipients are added to the prepared ordered mixture taken in a mortar and is granulated by wet granulation method using 15%w/v binding agent. The dried granules retained on sieve#44 when passed through sieve#22 together with 15% fines are mixed with weighed amounts of lubricants, glidants and spray dried flavors, these are further compressed in a single punch machine with maximum force to obtain a compact flat faced tablet lozenges.[2]

(ii) Preparation of compressed tablet lozenges of 10% drug adsorbate -Drug adsorbate (10%) are prepared by adding 1g of drug in boiling water taken in a petridish with constant stirring on a thermostatically controlled water bath. 10 g of activated magnesium trisilicate (obtained by vacuum drying at 100^{o}C and 720mmHg for 24 hours) is then added to the above drug mixture and mixed thoroughly to obtain a homogenous dispersion. Finally the mixture is oven dried at 70^{o}C until the moisture content got below 1.5%. This sieved free flowing powder is taken along with other excipients in a mortar and is then compressed to lozenges by wet granulation.[2]

(iii) Preparation of compressed tablet lozenges by using spray dried hybrid mixture of base and drug -Spray dried hybrid mixture is prepared by separately dissolving weighed quantity of base such as mannitol in distilled water**,** to which 10%w/w of drug is added with stirring. This homogenous solution is then fed into mini spray drier using a pressure atomizer through Rotating wheel with an atomizing air pressure of 5 kg/sq inch. The inlet temperature (140/160^{o}C), feed pump speed (2/4 ml/min), aspirator level (20-40) and concentrations of mannitol(10%-20%) used should be carefully optimized. Weighed quantity of this hybrid mixture is then taken along with other excipients in a mortar, and is then compressed to lozenges by wet granulation method [2].

(c). Miscellaneous methods: Candy lozenges are prepared by mixing dextrose solution and sugar syrup. The sugar syrup is prepared by mixing of water and sucrose. Dextrose solution was prepared by dissolving dextrose in very small quantity of water and heated it to 110^{0}C, till dextrose dissolves completely forming a viscous syrup. After this, prepared dextrose solution is poured in to the sugar syrup and heated to160^{0}C till the colour changed to golden yellow.Then the temperature is brought down to 90^{0}C,then drug polymer and other ingredient are added. The solution is poured into the mould having 2.8cm diameter and 6.5mm thickness. The prepared tablets are stored & wrapped in aluminium foils and stored in desiccators to prevent moisture uptake. The final weight of each lozenge is then calculated using weighing apparatus.[20, 28]

Characterization of Lozenges

(a). Weight Variation-

Weight variation test is performed by taking 20 formulated lozenges at random. Then individual weight of lozenges is determined and finally average weight is calculated by using formula--

Average weight = Individual weight of one lozenge/20.

(Then comparing individual weight to theaverage weight of lozenges.)

Weight Variation = [(Avg. weight-Individual Weight)/Avg. weight]*100.[23]

Table7: Limit for weight variation

Weight of the Tablet as per IP	**% Variation Allow**
<80mg	10%
80-250mg	7.5%
>250mg	5%
As per USP	**% Variation Allow**
<130mg	10%
130-324mg	7.5%
>324mg	5%

(b). Drug content –

Five lozenges are weighed individually and crushed using pestle mortar. Drug is diluted with 100 ml of distilled water. The drug content is determined by UV spectrophotometrically at suitable λ_{max} with blank lozenge extract as the reference.**[**23]

(c). Hardness-

The hardness of the lozenges is determined by using various types of hardness testers such as monsanto, erweka etc. The point at which lozenges break-down is known as the hardness of the lozenge.[29]

(d). Friability-

Friability is required to determine the fragility of lozenges which is required during transportation, shipping etc**.** The friability of lozenges is determined by using Rochelle apparatus, in which firstly accurate weight is taken out of 10 lozenges. These lozenges are placed in friability apparatus revolved at 25 RPM for 4 min. the individual lozenge is then once more weighed and the percent friability of lozenges was calculated using the formula-

% Friability = (Initial weight of 10 lozenges /Final weight of lozenges)*100. [29]

(e). Moisture content analysis-

Moisture content of the candy mass is analysed using different methods which include:-

i) Gravimetric Method- 1

g of sample is dried in hot air vacuum oven at 60-70^{0}C for about 12-16 hrs. After this, the sample is weighed again and moisture content was calculated using the formula.[26]

Moisture Content=Initial weight-Final weight

ii) Karl-fisher Titration-

A sample weighed to contain 10-250 mg water is placed into a titration flask and titrated by using Karl-fisher reagent.[26]

(iii) Azeotropic distillation method-

10-12g pulverized candy is taken and placed in 500ml flask and toluene (150-200ml) is added to it. Mixture is refluxed for 1-2 hours which ensures the collection of water in separate flask. The amount of water is calculated by this method and moisture content is determined [26]

(f) **Mouth dissolving time test-**

The time taken for candy to dissolve in to the mouth completely is known as mouth dissolving time test. This is determined by providing artificial environment by using USP disintegration apparatus, the lozenges are placed in each tube of this apparatus and time taken for the lozenges to dissolve completely is noted down. Phosphate buffer is used as the media for dissolving the lozenges**.[**23]

(g) *In-vitro* drug dissolution studies-

The rate of dissolution possibly is related to the efficacy of the tablet lozenge. Dissolution study is carried out by using USP type II paddle apparatus in 900 ml of Phosphate buffer operated at 100 rpm with temperature at 37±0.5^{0}C. Samples are withdrawn at 15 min interval and further replaced immediately with an equal volume of fresh buffer, then samples are analyzed by UV spectrophotometry. [23]

FACTOR AFFECTING DRUG RELEASE OF CANDIES. [30]

(i) Contact Time:

The local or systemic effect is based on the contact time of chewing gum in oral cavity. In a manner chewing time of 30 minutes was considered close to ordinary use.

(ii) Physicochemical properties of active ingredient:

Physicochemical property of active ingredient have main role in the effective lozenge formulation. Physicochemical property such as molecular weight, solubility, has important role. Water soluble drug start dissolving from mouth whereas lipid soluble drug in the intestine.

(iii) Inter individual variability:

The chewing frequency and chewing intensity both affect the drug release from chewing gum which may vary from person to person. According to European pharmacopeia 60 cycles per minute chewing rate for proper release of active ingredient prescribed *in- vitro.*

(iv) Formulation factor:

Composition, amount and type of gum base, method of formulation, time of processing, solubilizing

agents and softening agents may affect the rate of release of the active ingredient from lozenges.

Table No. 8: Different condition for stability studies

Temperature	RH%	Months
25°c	80%	6-12
37°c	80%	3
25°c	70%	6-12

(h) Stability studies-

The stability studies are carried out to evaluate the physical and chemical property of these dosage form. The estimation of drug content during long term storage of formulation which may cause change in different condition of temperature, humidity and other factor is necessary for safe and accurate drug content. The stability studies are carried out at different temperature and humidity which is defined by the ICH guidelines.[21]

(i) Microbial Assay-

Microbial assay is done to check contamination in raw material and finished product for the presence of bacteria, virus, mold or spores are checked for microbial contamination and Also machinery environmental cooling tunnel, and storage conditions. [4]

Microbial testing on laboratory should be included the following counts.

a. Salmonella
b. E. coli
c. Yeast and mold
d. Total coliform
e. Staphylococcus
f. Total plate

(j) Batch-Release Testing-

It is another most prominent and common quality control method and in process test. Batch-release testing includes:-

a. Uniformity of dose
b. Grittiness testing

The basic method involves the dissolution of lozenge into the running tap water medium until one-third or one-half of entire mass gets dissolved in medium taken. No grittiness must be felt when this dissolved material is rubbed between thumb and forefinger.

Test procedure is applicable for compressed tablet and also applies to lozenge mass. However, because the lozenge is intended to dissolve slowly in the mouth, typical disintegration and dissolution testing is inappropriate. Lozenges should be non-disintegrating, therefore as in case of normal tablet, there is no

need to carry out the disintegration studies in these formulations. Dissolution specifications development criteria should involve minimum and maximum time to physically dissolve in the medium provided, rather than minimum percent drug released in the maximum time interval. [1]

(k) Determination of Reducing Sugars

[i] Determination of Percentage of Reducing Sugars-

Standard anhydrous dextrose (3g) is taken and dissolved in 500ml water. After its complete dissolution the solution is boiled for 2 min. During boiling process, 2 drops of methylene blue is also added and titrated against 25mL of alkaline Fehling's solution with its composition being cupric tartrate, the interaction however results in giving a yellowish red end point.[11]

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

= reducing sugar factor for 3g dextrose

[ii] Determination of reducing sugars in the candy mass-

Approximately (10g) of candy material is dissolved in 250ml of water and titrated with 25 ml of Fehling's solution as was done previously for standard sample.

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

= Percent reducing sugar

(l) Water absorption ratio-

A tissue paper is folded twice and placed in a small petri-dish prefilled with 6 ml of water. A tablet is kept on the paper and the complete wetting time is measured. This wet tablet is again weighed. The Water absorption ratio is indicated by (R), which is calculated by using the below mentioned equation**. [**31]

$$\mathbf{R = (Wa- Wb/ Wb)\ 100}$$

Wa = final weight of tablet after water absorption.

Wb= initial weight of tablet before water absorption.

(m) Thickness and Diameter-

Thickness and diameter of lozenges measured by using Vernier Callipers. It is determined by checking the thickness and diameter of ten lozenges. The thickness of the each lozenge must not fall outside ± 5% of the standard value determined. [26]

Table 9: Marketed Candy Products

Sl. NO	Product	Main Ingredients	Other Ingredients	Indication	Marketed by
1	VICKS®	Menthol	Ascorbic acid, citric acid, eucalyptus oil, FD&C Blue No. 1, FD&C Red No. 40, flavor, liquid glucose, sucrose	sore throat	Procter and Gamble manufacturing company
2.	THERA ZINC®	Zinc (Gluconate)	Vitamin A (Acetate) 500 IU, A proprietary blend of Slippery Elm Bark (Ulmus fulva) family Echinacea in ratio of 4:l, Propolis, Elderberry, Larch and Mullein. Natural flavors.	common cold and flu	Quantum health care
3.	NICORETTE®	Nicotine	aspartame,calcium-polycarbophilflavor, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, xanthan gum, magnesium stearate	smoking cessation	Perrigo company
4.	STREPSILS®	Amyl-metacresol-dichlorobenzyl alcohol	Hexylresorcinol, sucrose, glucose, levomenthol, blackcurrant flavour (contains propylene glycol), carmoisineedicol (E122), patent blue V (E131).	Sore throat and blocked nose	Reckitt Benckiser healthcare ltd.
5	CLOTRIMAZOLE LOZENGE®	Clotrimazole	Crosscarmellose, Sodium Dextrates,magnesium stearate, Cellulose Microcrystalline, Povidone	Oral thrush	Perrigo company
6.	SUCRETS®	DextromethorphanHydrobromide	Corn Syrup, D&C Yellow10, Hydrogenated Palm Oil, Menthol, N&A Honey Lemon flavor, Sugar	Sore throat	Insight Pharmaceuticals

7.	CEPACOL®	Menthol, benzocaine	Cetylpyridinium chloride (Ceepryn®), glucose, peppermint oil, propylene glycol, sucrose, yellow 10	Sore throat	Combe incorporations
8.	VIGROIDS®	Liquorices	Maize starch, menthol, kaolin, tragacanth, eucalyptus oil, peppermint oil, tolu tincture	Expector-ant	Ernest Jackson and Company Ltd.
9.	CHLORASEPTIC®	Benzocaine	Corn Syrup, FD&C Red #40, Flavor, Glycerin, Soy Lecithin, Sucrose, Water	Relief of minor sore throat and mouth pain	Prestige Brands lnc.
10.	LOCKETS®	Eucalyptus and menthol	Sugar, Glucose syrup, Honey, Glycerol, Citric Acid, Vitamin C, Monopropylene Glycol, Colors E122 and E142.	Nasal congestion and sore throat	Wrigley Company
11.	KOFLET-H®	Madhu	Haritaki, Trikatu,	Alleviate cough and quickly	Himalaya Herbal Healthcare

			Kulanjana (Alpiniagalanga) Khadira (Acacia catechu) Oils of :- Lavanga, Sukshmaila (Elettariacardamomum), Darusita (Cinnamomumzeylanicum, Sugar base q.s	relieves throat irritation	
12.	SUALIN®	Glycyrrhizaglabra	Aadhatodavesica, Ocimum sanctum, mentha arvensis, Pimpenellaanisum, citriodorazeylanicum, piper cubaba.	Influenza, bronchitis, sore throat, cold and cough, congestion of head and lungs	Hamdard (WAKF) Laboratories

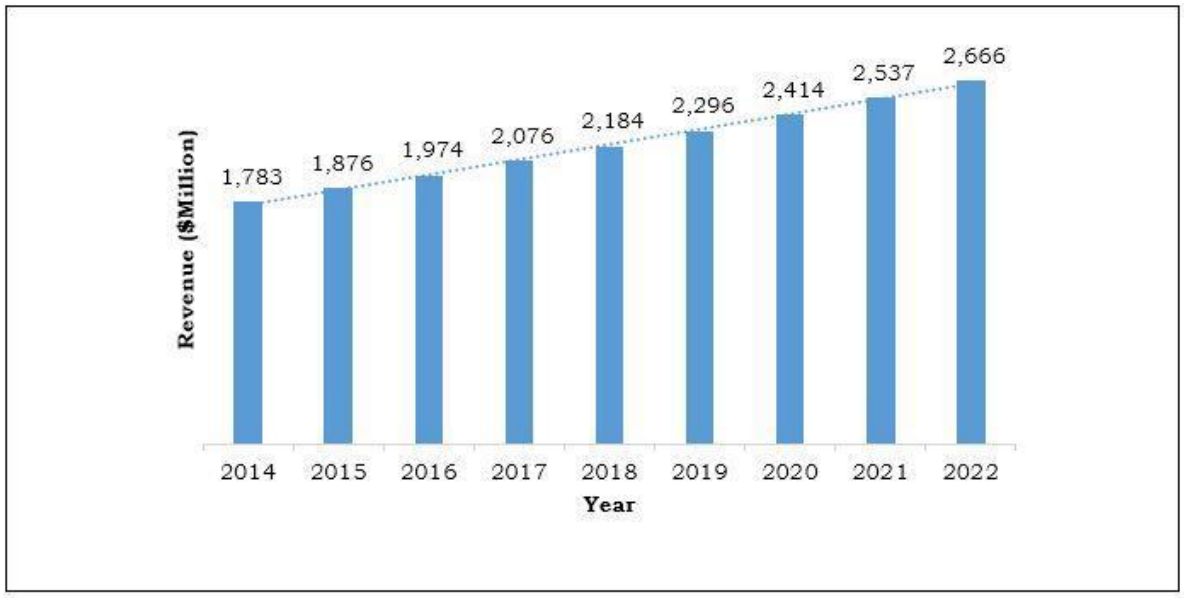

Figure 2: Current Marketting Trends of Sugar Confectionaries

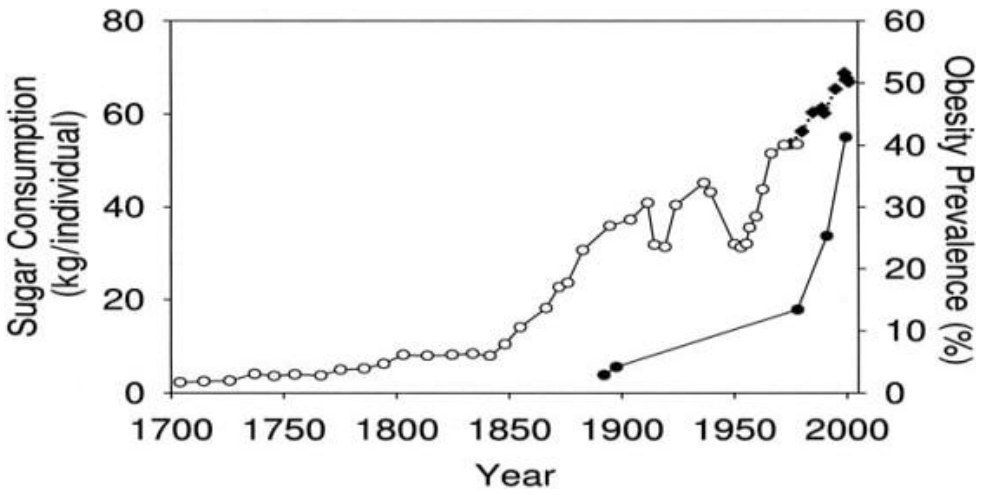

Figure.3- Obesity Index of UK over the years

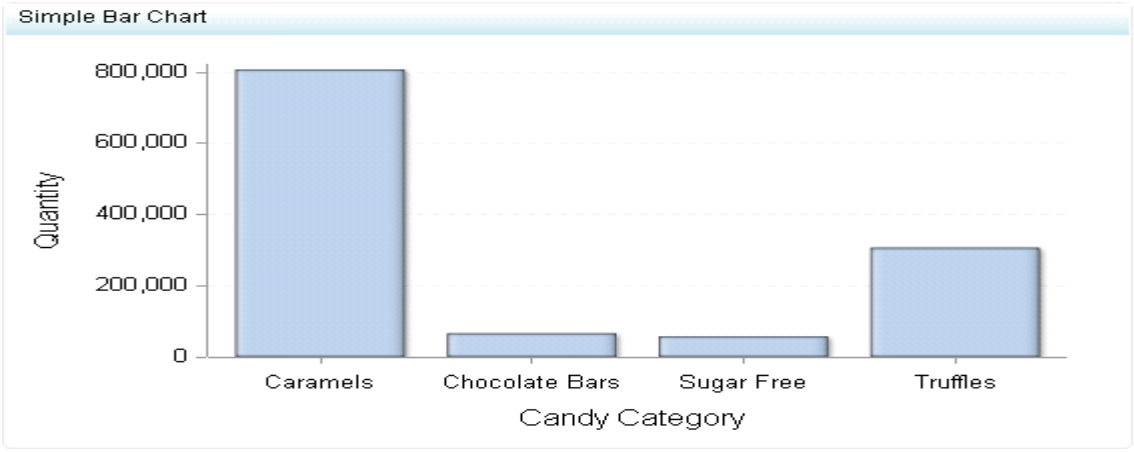

Figure 4- Sales of candies in different categories on an annual basis

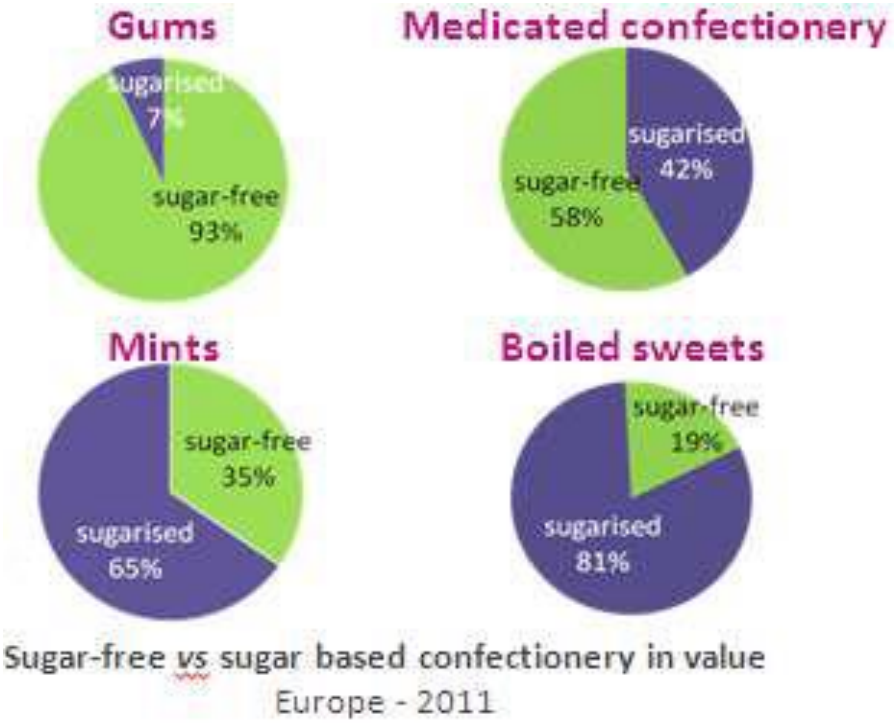

Figure 5: Comparison between sugarised and non-sugar based confectionaries in value

Future Trend In Candies

Lozenges not only offer clinical benefits but also are an attractive, discrete and efficient drug delivery system. A few decades ago, the only surgical procedure was established and available for treatment of some diseases but now lozenges in novel drug delivery system frequently used. Generally, it takes time for a new drug delivery system to establish itself in the market and gain acceptance by patients, however lozenges are believed to manifest its position as a convenient and advantageous drug delivery system as it meets the high quality standards of pharmaceutical industry and can be formulated to obtain different release profiles of active substances. The application scope for medicated lozenges, however, is wide and more products will become available. Medicated candies is a valid alternative to standard, chewable or orally disintegrating tablet presentations.[26]

Sugar- Free Candies (Need of The Hour)

Sugar is generally considered as the high rich calorie value food which often lead to obesity and thus being an active constituent of lozenge formulation leads to rejection of the lozenges formulation.

Also, the diabetic population disapproves of the usage of these formulations due to same reason this demerit has resulted in an increment of usage of sugar-free lozenges over the years.

- The sugar-free chewing gum market – which incidentally first started as sugar-based and then switched completely to sugar-free – provides other confectionery segments with an interesting perspective on sugar-free market share development.
- In addition to chewing gum, sugar-free medicated confectionery – with its inherent health benefits – is also well positioned at 58% market share.
- At the same time, sugar-free mints, at 35%, demonstrate that the sugar-free trend is gaining momentum.

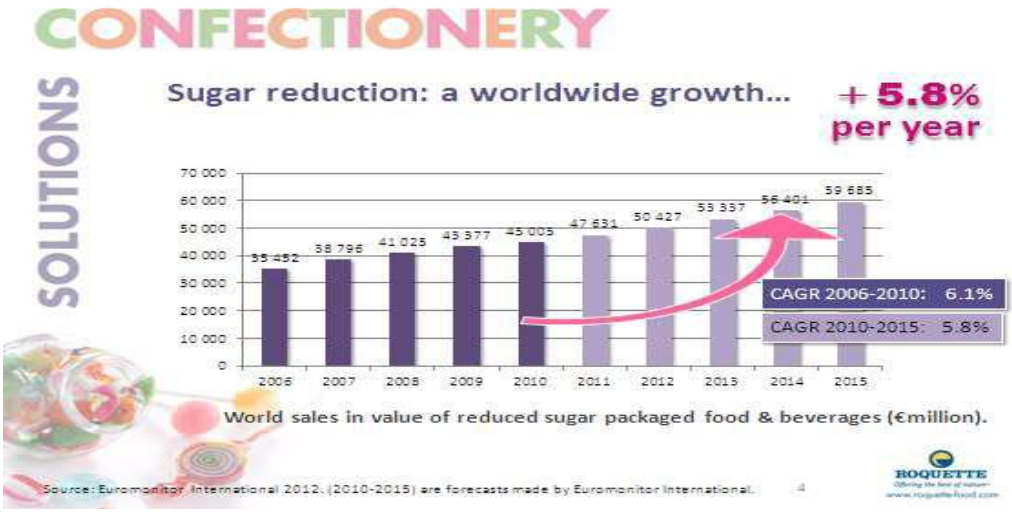

Figure 6- World Sales of reduced sugar packaged foods and beverages (in € million)

Conclusion

Candies or Lozenges are easy to formulate and can also be termed as time saving formulations as relatively low amount of time is required for their manufacturing. It is one of the most organoleptically accepted formulations particularly for the pediatric patients thus ensuring its idealness for the pediatric patient. The advantage of lozenges is that it is used for patient compliance, convenience and comfort for the efficient treatment especially local infection (at low doses). It also gives the immediate onset of action and also reduce dosage regimen. This formulation can also be rendered as most economic one. Lozenges are mostly used for the localized effect, and also be used for the systemic effect if the drug is absorbed through the buccal lining. Most of the lozenges are available in form of OTC "over the counter" marketed formulation. It is easy to administer for pediatric and geriatric patients. Lozenges enjoy an important position in pharmaceuticals and will continue to remain at the same in future.

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