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Secundum Artem

Current & Practical Compounding Information for the Pharmacist.

TROCHES AND LOZENGES

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INTRODUCTION

Lozenges, or troches, are experiencing a renewed popularity as a means of delivering many different drug products. They are used for patients who cannot swallow solid oral dosage forms as well as for medications designed to be released slowly to yield a constant level of drug in the oral cavity or to bathe the throat tissues in a solution of the drug.

Lozenges historically have been used for the relief of minor sore throat pain and irritation and have been used extensively to deliver topical anesthetics and antibacterials. Today they are used for analgesics, anesthetics, antimicrobials, antiseptics, antitussives, aromatics, astringents, corticosteroids, decongestants, and demulcents and other classes and combinations of drugs.

Both chewing gum and lozenges may be considered as alternatives to current dosage forms. They are easy to handle, the dose has been apportioned, and the excipients have a demulcent effect on a sore throat since the ingredients are released slowly and spread uniformly over the affected mucosal membrane.

An advantage of the lozenge dosage form is that it is easy to administer to both pediatric and geriatric patients. It has a pleasant taste and will extend the time a quantity of drug remains in the oral cavity to elicit a specific effect. Also, it can be prepared extemporaneously by pharmacists with a minimal amount of equipment and time.

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One disadvantage of the lozenge dosage form is that it mistakenly could be used as candy by children. Parents should be cautioned not to associate medications with candy and to keep the product out of the reach of children.

TYPES AND DEFINITIONS

Lozenges are various-shaped, solid dosage forms usually containing a medicinal agent and a flavoring substance, intended to be dissolved slowly in the oral cavity for localized or systemic effects. They are also called troches or pastilles. Pastilles have a softer texture and a high percentage of a sugar or a combination of a gelatin and sugar.

Many lozenges have hard candy bases of sugar and syrup and often incorporate an adhesive substance such as acacia. Commercial lozenges may be made on a tableting machine using high compression pressures. Lozenges are designed to dissolve slowly in the mouth. They are designed to dissolve and not to disintegrate. Ingredients should be heat-stable if they are to be incorporated into extemporaneously-prepared lozenges.

Recently, soft lozenges and chewable lozenges have been re-introduced into pharmacy and are enjoying increased popularity. The soft lozenges generally have a polyethylene glycol base and the chewable lozenges have a glycerinated gelatin base. These usually are chewed and are a means of delivering the product to the gastrointestinal tract for systemic absorption.

Hard Lozenges

Hard candy lozenges are mixtures of sugar and other carbohydrates in an amorphous (noncrystalline) or glassy condition. These can be considered solid syrups of sugars and

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usually 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. A primary disadvantage of hard candy lozenges is the high temperature required for their preparation. Hard candy lozenges generally weigh between 1.5 and 4.5 gm.

Excipients such as sorbitol and sugar have demulcent effects, which relieve the discomfort of abraded tissue resulting from irritation due to cough and sore throat. A portion of the active drug product actually may be absorbed through the buccal mucosa, thereby escaping the first-pass metabolism which occurs when a drug is swallowed and absorbed through the gut.

Soft Lozenges

Soft lozenges have become popular because of the ease of extemporaneous preparation and applicability to a wide variety of drugs. The bases usually consist of a mixture of various polyethylene glycols, acacia or similar materials. One form of these soft lozenges is the pastille, which is defined as a soft variety of lozenge, usually transparent, consisting of a medication in a gelatin, glycerogelatin or acacia:sucrose base. Pastilles may be colored and flavored and can be either slowly dissolved in the mouth or chewed, depending upon the action desired for the particular incorporated drug.

Chewable Lozenges (Gummy Novelty-Shaped Products)

Soft, chewable candies have been on the market for a number of years. They are very highly flavored 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. They are relatively easy to prepare extemporaneously. The most difficult part involves the preparation of the gelatin base, described below. These are especially used for pediatric patients and are a very effective means of administering medications for gastrointestinal absorption and systemic use.

PREPARATION

Lozenges/Troches are prepared by molding a mixture of various carbohydrates to form candies, by molding a matrix to form a soft lozenge, or by molding a gelatin base into a chewable mass.

Hard lozenges are usually prepared by heating sugar and other components to a proper temperature and pouring into a mold or pulling the mass out into a ribbon while cooling, then cutting to the desired length. A commercial method is to compress the materials into a very hard tablet.

Soft lozenges and chewable lozenges are usually prepared by pouring a melted mass into molds. Another method, dependent upon the ingredients, is to pour the mass out to form a sheet of uniform thickness. The lozenges can then be "punched out" with a punch of the desired shape and size.

Molds used in the preparation of lozenges/troches must be calibrated to determine the weight of the lozenge using the particular base of

interest. This can be done as follows.

1. Prepare the lozenge mold and confirm that the cavities are clean and dry.
2. Obtain and melt sufficient lozenge base to fill 6 to 12 molds.
3. Pour the molds, cool and trim, if necessary.
4. Remove the lozenges and weigh.
5. Divide the total weight by the number of blank lozenges prepared to obtain the average weight of each lozenge for this type of particular base.

Use this weight as the calibrated value for that specific mold using that specific lot of lozenge base. The powders contained in the lozenges may also occupy a specific volume and an adjustment may need to be made in the quantity of base used. These "dosage replacement calculations" have been covered in a previous issue of Secundem Artem (Volume 3, Number 4).

PACKAGING

Hard candies are hygroscopic and usually prone to absorption of atmospheric moisture. Considerations must include the hygroscopic nature of the candy base, storage conditions of the lozenges, length of time they are stored and the potential for drug interactions.

These products should be stored in tight containers to prevent drying. This is especially true of the chewable lozenges that may dry out excessively and become difficult to chew. If a disposable mold with a cardboard sleeve is used, it is best to slip this unit into a properly labeled, sealable plastic bag.

STORAGE

These preparations should be stored away from heat and out of the reach of children. They should be protected from extremes of humidity. Depending on the storage requirement of both the drug and base, either room temperature or refrigerated temperature is usually indicated.

DISPENSING

The patient should receive counseling 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 of children.

FLAVORING

For hard lozenges, the emphasis is on the slow, uniform release of the medication directly onto the affected mucous membrane. This presents an additional challenge to the compounding pharmacist to develop flavor blends that effectively mask any unpleasant principles contributed by the medications, while maintaining a smooth lozenge surface texture as the tablet slowly dissolves. If the incorporated medication has no significant taste, flavoring will not be a problem. However, if the medication has a strong, disagreeable taste, special emphasis should be placed on minimizing the taste in order to enhance patient compliance.

Flavor is a very complex phenomenon that is a combination of the senses of taste, touch, smell, sight and sound. The first of these, taste, is made of four primary tastes: sweet, bitter, sour and salty. We are generally more sensitive to odors than to tastes and the level of odor required for the elderly may be 3-5 times greater than that required for young people. Females tend to have a greater sensitivity to odors than do males. Taste and smell are altered in many disease states.

Some correlations can be made between flavors/odors and chemical structure. For example, a sour taste is associated with hydrogen ions, saltiness with both anions and cations present, bitterness with high molecular weight salts, sweet with polyhydroxyl compounds/polyhalogenated compounds and alpha amino acids, a sharp, biting taste with unsaturation, a camphoraceous odor with a tertiary carbon atom, a fruity odor with esters and lactones, and a pleasant odor with ketones. The causative factors for taste include the following: a HOT taste is due to a mild, counterirritant effect, an ASTRINGENT taste is due to tannins and acids, COARSENESS/GRITTINESS is due to texture, and COOLNESS is due to a negative heat of solution.

In flavor formulation development, there are usually the requirements for an immediate flavor identity, a rapid full flavor development, compatible mouth feel, no "off" notes, and a short aftertaste. Some techniques commonly used in flavoring include blending, overshadowing, physical methods, chemical methods, and physiological methods. A flavor selection guide is shown in Table 1.

Blending: Blending incorporates the use of a characteristic common to both the flavor and drug, for example the use of a fruit flavor to blend in with a sour/acid taste (orange flavor to blend with ascorbic acid). Salty/sweet/sour flavors can be used to blend with a bitter taste. Also, the use of a slight salty taste will actually decrease sourness and increase sweetness. It has also been found that adding a sour flavor may help overcome a bitter taste.

Overshadowing: Methyl salicylate and glycyrrhiza, with their strong essences, can overshadow or overpower many products.

Physical Methods: Physical methods include the formation of insoluble compounds, emulsification of oils, effervescence, high viscosity fluids and the coating of tablets. Insoluble compounds can be formed and result in a minimal taste due to the drug. The drug must be in solution for it to be "tasted"; therefore, drugs in suspension usually do not impart taste. Poorly tasting oils can be incorporated into the internal phase of an oil-in-water emulsion and the external aqueous phase can be sweetened and flavored. This is the principle behind products such as cod liver oil emulsion, castor oil emulsion, etc., where the patient primarily tastes the sweetened, flavored external aqueous phase upon administration.

FLAVOR SELECTION GUIDE

Taste	Flavors That Can Be Used
Salty	Butterscotch, Maple, Nutty, Buttery, Spice
Bitter	Wild Cherry, Licorice, Chocolate Mint, Grapefruit, Coffee, Cherry, Peach, Raspberry, Orange, Lemon, Lime
Acrid/ Sour	Raspberry, Fruits, Berries, Acacia Syrup
Oily	Peppermint, Anise, Wintergreen
Sweet	Fruit, Berry, Vanilla
Acid	Citrus
Metallic	Berries, Mint, Grape, Marshmallow

Table 1

Chemical Methods: Chemical methods include adsorption and complexation of the active drug to a material, resulting in a loss of the undesirable taste characteristics.

Physiological Methods: Physiological methods include utilizing the anesthetic effect imparted by menthol and mint, which can be used to assist in making a taste more palatable.

Flavoring materials are very complex mixtures. The following table illustrates the number of separate chemicals that may be contained in both natural and artificial flavors.

	Number of Components of Flavors	
	Natural	Artificial
Cherry	>70	>20
Banana	>150	>17
Grape	~225	>18
Strawberry	>130	>36
Raspberry	>60	>17

Many natural flavors do have a "prominent" ingredient. For example, the primary active constituent in cherry is benzaldehyde, in banana, iso-amylacetate, in spearmint, l-carvone and in orange, lemonene.

Flavors also share many of the same characteristics as active drug products of which the compounding pharmacists must be aware. For example, they can adsorb to plastics, filters and filter aids.

In general, the quantity of flavoring agent added to medicated lozenges is about 5 to 10 times that used in candy lozenges in order to compensate for the flavor of the medication.

Addition of the flavoring agent (an oil), if it is immiscible with the base, can be accomplished by dissolving the oil in glycerin and incorporating the glycerin solution into the product. The same technique can also be used to incorporate an oily drug into a lozenge. The solvent technique often uses a ratio of 1 part of solvent, such as glycerin, for 3 to 5 parts drug.

PRESERVATIVES

Since these are solid dosage forms, there usually is no need to incorporate preservatives. However, since hard candy lozenges are hygroscopic, the water content may increase and bacterial growth may occur if they are not packaged properly. Since the water that is present would dissolve some sucrose, the resulting highly concentrated sucrose solution is bacteriostatic in nature and would not support bacterial growth.

A few comments are in order concerning the flavors and effects of preservatives. For example, a 0.08% solution of methylparaben has an odor described as "floral", "gauze pad", or "face powder" sweet. A 0.015% solution of propylparaben has an effect that is tongue numbing, producing a slight sting and a minimal aroma. A 0.125% butyl paraben solution has the least aroma of all.

Preservatives may have a tendency to partition into flavors since preservatives are not always very water soluble and most flavors are oily in nature.

EXAMPLE FORMULATIONS

Example formulations are presented for discussion purposes only to illustrate the differences in the types of lozenges and their applications. These formulas can be adjusted based on the quantity of active drug to be used.

Hard Lozenges

Rx		
	Powdered Sugar	42 gm
	Light Corn Syrup	16 mL
	Distilled Water	24 mL
	Active Drug, Example	1.0 gm
	Mint Extract	1.2 mL
	Food Coloring, Green	qs

Combine the Sugar, Corn Syrup and Water in a beaker and stir until mixed well. Cover the mixture and heat on a hot plate at a high setting until the mixture boils and continue boiling for two minutes. Uncover and remove from heat at 141° C. Do not stir the mixture until the temperature drops to 129° C. Quickly add the Active Drug, Mint Extract and Food Coloring and stir until well-mixed. Using a vegetable spray, coat the mold to be used. Pour the melt into the molds, cool, package and label.

Soft Lozenges

Rx		
	Steroid Linguets *** mg	
	Fattibase® (Paddock)	76 gm
	Steroid Powder	*** gm
	Acacia	3 gm
	Cinnamon Oil	5 gtts
	Artificial Sweetener	14 gtts

Melt the Fattibase® (Paddock) at about 40° C. Add the Acacia powder followed by the Steroid and mix well. Add the artificial sweetener and the Cinnamon Oil and mix well. Use Sweeta® brand since Equal® or Nutrasweet® may break down at high temperatures. Pour into 1 gram molds and place in a refrigerator to cool and harden. Store in a refrigerator.

Rx		
	Polyethylene Glycol Troches	
	Polyethylene Glycol 1000	10 gm
	Active drug, example	1 gm
	Sweeta® Sweetener	20 packets
	Mint extract	1 mL
	Food Color	2 drops

Melt the Polyethylene Glycol 1000 on a hot plate to about 70° C and gradually add the Active Drug powder and the Sweeta® Sweetener with stirring. Add the coloring and flavoring and pour into troche molds. Allow to cool at room temperature.

Rx	Polyethylene Glycol Troches With Suspending Agent Makes 24 troches with 200 mg active drug in each.	
	Polyethylene Glycol 1000	34.5 gm
	Active Drug, example	4.8 gm
	Silica Gel	0.37 gm
	Acacia	0.61 gm
	Nutra-Sweet® (aspartame)	0.73 gm
	Flavor	5 drops

Blend the powders together until uniformly mixed. Heat the Polyethylene Glycol 1000 until melted at approximately 70° C. Add the powder mix to the melted base and blend thoroughly. Cool to less than 55° C, add the Flavor and mix well. Pour into troche or cough drop molds, cool, package and label. This formulation is based on a mold that weighs approximately 1.8 gm. The formula can be adjusted to other mold weights.

Rx		
	Powdered Sugar Troches	
	Powdered Sugar	10 gm
	Active drug example	1 gm
	Acacia	0.7 gm
	Water	q.s.

Mix the Acacia and Water together in a mortar to form a mucilage. Sift the Powdered Sugar and Active Drug together and gradually add sufficient mucilage to make a mass of the proper consistency. Roll the mass into the shape of a cylinder and cut into 10 even sections (approximately twice the length of the diameter). Allow to air dry, package and label.

Chewable Lozenges

Gelatin Base:	
Glycerin	155 mL
Gelatin	43.4 gm
Water	21.6 mL
Methylparaben	0.44 gm

Heat a water bath to boiling. In a beaker, combine the Water, Glycerin and Methylparaben, stir and heat for five minutes. Over a three-minute period, very slowly add the Gelatin while stirring until it is thoroughly dispersed and free of lumps. Continue to heat for 45 minutes, remove from heat, cool and refrigerate until used.

Product:	
Gelatin Base	43 gm
Bentonite	800 mg
Aspartame	900 mg
Acacia Powder	720 mg
Citric Acid Monohydrate	1.08 gm
Flavor	14-18 drops
Active Ingredient	—

Calibrate the particular mold to be used for this product. Melt the Gelatin Base using a water bath. Triturate the powders together and add to the gelatin base melt and thoroughly mix until evenly dispersed. Add the desired Flavor and mix. Continuously mix and pour the melt into the pediatric chewable lozenge molds and allow to cool. If the mixture congeals while pouring, it may be necessary to reheat and then continue pouring.

DISCUSSION

Concerning salivary kinetics, there is approximately a 1.07 mL volume of saliva resident in the mouth before swallowing and about 0.71 mL after swallowing. The baseline flow rate for saliva is about 0.3 mL/minute that may be increased to about 10.6 mL/minute when stimulated. The frequency of swallowing is about 0.6 to 2.3 times per minute. In general, the rate of removal of dosage forms from the mouth is in the following order, from the most rapid to the slowest: tablets/capsules, solutions, suspensions, chewable tablets, lozenges/troches.

The type of medication prepared as a lozenge/troche is limited only by flavor, dose limitations, and/or chemical incompatibility. Some materials are so unpalatable or irritating that they are unsuitable for this type of administration. The following is illustrative of different active ingredients that are used in lozenges.

Benzocaine: The usual dose of benzocaine is in the range of 5 to 10 mg per lozenge. It is extremely reactive with aldehydic components of candy base and flavor components and as much as 90 to 95% of available benzocaine may be lost when added to a candy base, but a polyethylene glycol base is compatible.

Hexylresorcinol: The dose of hexylresorcinol is about 2.4 mg per lozenge. It is somewhat susceptible to reaction with aldehydic components. There are no flavoring or mouth-feel problems associated with it because of its low dose and lack of any appreciable flavor.

Dextromethorphan: The dose of dextromethorphan HBr is about 7.5 mg per lozenge. It is easy to incorporate into a candy base because of its melting point (122˚-124˚ C) and solubility (1.5 gm in 1000 mL of water). It is compatible with most flavors and is stable over a wide pH range. However, it does have a bitter taste, an anesthetic mouth-feel and an unpleasant aftertaste. Masking doses greater than about 2.0 mg per lozenge requires special considerations.

Phenylpropanolamine: The dose of phenylpropanolamine is about 18.5 mg per lozenge.

Incorporating about 20 mg in a lozenge results in a product with an acceptable mouth-feel which is not difficult to flavor because of the low level of medication per lozenge.

Hard Lozenges

All hard candy type lozenges eventually become grainy but the speed at which this occurs is dependent upon the ingredients that are used. The incorporation of corn syrup solids at a greater than 50% concentration decreases the graining tendencies but can increase moisture absorption tendencies which increase product stickiness and interactions of medicaments. Using greater than 70% sucrose solids tends to increase graining tendencies and the rapidity of crystallization. Formulations that contain between 55 and 65% sugar and 35 to 45% corn syrup solids generally offer the best compromise among the resistance to graining, reduction of moisture absorption and realistic preparation time.

Acidulents, such as citric, tartaric, fumaric and malic acid may be added to candy base to strengthen the flavor characteristics of the finished product and to control pH to preserve the stability of the incorporated medication. Regular hard candy has a pH of about 5.0 to 6.0 but with the addition of acidulents, it may be as low as 2.5 to 3.0. Calcium carbonate, sodium bicarbonate and magnesium trisilicate can be added to increase the lozenge pH to as high as 7.5 to 8.5.

Soft Lozenges

Soft lozenges are similar to a historical form of medication that is making a comeback: the "confection". Confections are defined as heavily saccharinated, soft masses containing medicinal agents. The improvement in their current use is largely due to the use of polymers (polyethylene glycols) as the matrix for the dosage form. They are easy to use, convenient to carry, easy to store (room temperature), and are generally pleasant tasting. Polyethylene glycol-based lozenges may have a tendency to be hygroscopic and may soften if exposed to high temperatures. Consequently, storage in a cool, dry place should be recommended.

Chewable Lozenges

One of the more popular lozenges for pediatric use is the chewable lozenge, or "gummy-type" candy lozenge. The gelatin base for these chewable lozenges is similar to the former Glycerin Suppositories, or Glycerinated Gelatin Suppositories, which consisted of 70% glycerin, 20% gelatin and 10% purified water. Some of the earlier pastilles consisted of a gelatin or a glycerogelatin base. These gelatin-based pastilles were prepared by pouring the melt into molds or out onto a sheet of uniform thickness. The dosage forms were then "punched out" using various shaped punches. The last step often included the "dusting" of the product with corn starch or powdered sugar to decrease tackiness. These pastilles should be stored in a refrigerator, depending upon the active drug contents.

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