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TECHNOLOGICAL STUDY OF LOZENGES

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Abstract— Recently, herbal supplements have been widely used to treat upper respiratory illnesses, colds, and sore throats. Lozenges are one of the most widely used forms of medicine. The dosage form is prepared to have a pleasant taste and has a large number of advantages in the pharmaceutical market.The lozenge has a direct effect on the oral mucosa, has partial and general action, increases bioavailability, reduces gastric irritation, does not pass through the liver, does not need to be swallowed, and has many advantages such as ease of use and ease of production and storage. Currently, only herbal medicines such as Koflet, Koflet-N and Dr. Mom, which are used for the needs of the population of Mongolia, are imported. Therefore, there is a need to study the possibility and output of import-substituting products at home. We use *Glycyrrhiza uralensis* Fish, *Eugenia caryophyllata* Thunb, and *Kaempferia galangal*, which are widely used in Mongolian traditional and modern medicine to clear phlegm, relieve cough, heal wounds, and relieve pneumonia. The goal is to develop a technological scheme for drug preparation. We developed a technological scheme for lozenge containing liquorice. Some criteria for lozenges quality: appearance, base quality, solubility, average weight (n = 5) M = 2.5 ± 0.02, weight variation (± 4%), strength (n = 5) M = 99.2 ± 0.01, the moisture content (n = 5) was found to be M = 0.18 ± 0.01 $p < 0.05$.

Keywords: liquorice, expectorant, suppress coughing, lozenge, technological scheme

Background

Respiratory diseases are one of the five leading causes of morbidity in our country, and according to statistics (2008-2019), they have increased by 2.5% in recent years. As a result, there is a growing demand for drugs for this disease. [1]

Respiratory infections are spread regardless of the living environment, social conditions, lifestyle and standard of living. Because the respiratory system is in constant direct contact with the environment, respiratory infections are always at the forefront of other infections.[2,3]

Recently, herbal supplements have been widely used to treat upper respiratory illnesses, colds, and sore throats.[4]Lozenges are one of the most widely used forms of medicine.[5] This form of the drug has a partial therapeutic effect rather than a general effect, and the addition of various active substances improves the overall therapeutic effect.[6]

The dosage form is prepared to have a pleasant taste and has a large number of advantages in the pharmaceutical market. [7]

Herbal medicines used for the needs of the Mongolian population, such as Koflet, Koflet-N, Dr. Mom, Woods, Timiar, and Linkas, are currently imported only.[7,8]

Therefore, this topic was chosen in order to study the possibility and output of domestically produced import-substituting products.

We use *Glycyrrhiza uralensis*, *Eugenia caryophyllata*, and *Kaempferia galangal*, which are widely used in Mongolian traditional and modern medicine to clear phlegm, relieve cough, heal wounds, and relieve pneumonia.[9,10] The goal is to develop a technological scheme for drug preparation.

Methods

High-performed liquid chromatography (HPLC) and PMB-53 moisture meters were used to test lozenges quality characteristics. Suchitra Pundir*et al.* methods were used to develop the lozenges technology.

Results

Table 1. Results of determination of acute toxicity (LD50) of dried extract of *Glycirrhiza uralensis*

Dosage	Number of dead animals	Number of live animals	Percentage of dead animals (%)	a+b	M-n	(a+b)(M-n)
4600мg/кg (n=4)	0	4	0	-	-	-
4700мg/кg (n=4)	2	2	50	9300	50	465000
4800мg/кg (n=4)	3	1	75	9500	25	237500
4900мg/кg (n=4)	4	0	100	9700	25	242500

Calculation of the toxicity of the test preparation (LD50):

$$\mathbf{LD_{50}}=\sum\frac{(a+b)(M-n)}{200}=\sum\frac{465000+237500+242500}{200}=\frac{945000}{200}=4725\ \frac{mg}{kg}$$

According to the results of the above toxicity study, the dose of 4725 mg/kg according to KK Sidorov's classification is relatively harmless.[11,18]

Maximum non-adverse dose (NOAEL):

$$\mathbf{NOAEL}=\frac{LD50}{10}=\frac{4725mg/kg}{10}=472.5\ \text{mg/кg}$$

The highest non-adverse dose of the study was 94.5 mg/200 g per day for animals and 76.6 mg / kg per day for humans.

The amount determined by the composition of the base of the lozenges

The composition of the base was determined by comparing the results of researchers in other countries.[12]

Table 2. Ingredients for the preparation of the base of the lozenges

Ingredients for base preparation	**Suchitra Pundir*, Abhay Murari Lal Verma research**	**Result of current research**
Base	Dextrose, sucrose, maltose, lactose	Sugar
1.Sugar	Mannitol, sorbitol, polyethylene glycol 600	(Dextrin, Maltose, Glucose)
2.Sweetener		- Molasses
3.Filler	Calcium phosphate, calcium sulfate, lactose	
Lubricants	Magnesium stearate and calcium stearate	-

Binders	Hay tree, corn syrup, sugar syrup, gelatin, polyvinyl prolidene, tragacanth, methyl cellulose	-
Coloring agent	Lacolin, FD and C color, orange color, red color	Concentrated sea buckthorn juice
Flavoring	Menthol, eucalyptus oil, cherry menthol	Menthol
Thickening agents	Milk protein, egg yolk, gelatin, xanthine, pectin	-
Moisturizers	Glycerin, propylene glycol, sorbitol	
The main active ingredient Dried licorice extract 9%		Excipients *Eugenia caryophyllata*Ginger Menthol Sea buckthorn juice

As shown in Table 1, sugar, molasses, concentrated sea buckthorn juice as a colorant, and menthol, which has a disinfecting effect with a flavoring agent, were used as the basis for the preparation.

A. (2.5 g×16) Lozenge base:

Distilled water -20 ml
Sugar-50 g
Molasses-50 ml
Concentrated sea buckthorn juice - 20 ml

Preparing the base:

Select a base cooking pot on an induction oven, add 20 ml of distilled water and boil at 150°C, then add 50 g of sugar and 50 ml of molasses and mix well. Then add 20 ml of concentrated sea buckthorn juice, mix well and the base is ready. We determined the appropriate cooking temperature for the base through four experimental studies. The following table shows the optimum cooking temperatures for the base.

Table 3. Determining the optimum cooking temperature for the base

Experiment	Experiment-1	Experiment-2	Experiment-3	Experiment-4
Base cooking temperature (°C)	**300°C** 20-25 min	**250°C** 20-25 min	**200°C** 20-25 min	**150°C** 20-25 min
Color, odor, taste, uniform viscosity	It is dark brown in color, has a burnt odor, has a burnt taste and high viscosity	It is dark brown in color, has a burnt odor, has a burnt taste and high viscosity	Brown, burnt taste, odor, low viscosity	It is brownish-yellow in color, has no burnt taste, has a sweet taste, and has relatively low viscosity

The table above shows that Experiment 4 is the most suitable.In other hand, it is brownish-yellow in color, has no burn taste, has a sweet taste, and has a relatively low viscosity.

The technical requirements for the foundation are shown in the following table.

Table 4. Requirements for the base of the lozenges

№	Description	Technical requirements	Allowable amount	Results
1	Heavy metal mixture	MNS 2850:1980	Less than 0.01%	0.006%
2	Density	National Pharmacopeia article, 521 Drug technology Vol 1	1.29-1.31	1.3

The table above shows that the base of the peat meets the technical requirements.

B. The composition of the lozenges

In our study, we selected dried licorice extracts with expectorant and cough suppressants based on the composition of well-known and imported herbal medicines such as Dr. Mom, Koflet, and Koflet-H, which are widely used in medicine.

Ingredients in 1 bag:

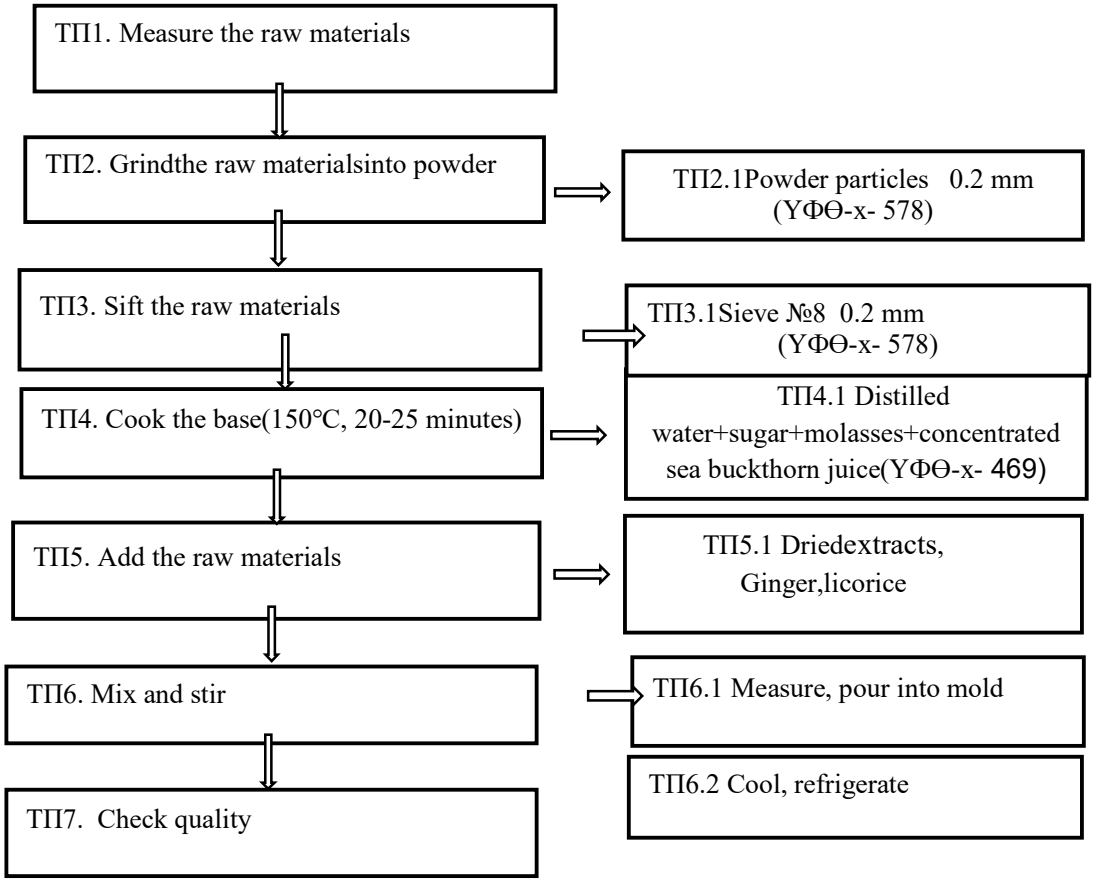
- Dried licorice extract (9%) 0.4 g
- *Eugenia caryophyllata*powder 0.2 g
- Ginger powder 0.2 g
- Menthol-0.5 g
- Sugar-0.5 g
- Molasses-0.7 g

Table 5. Requirements for raw materials and auxiliary materials to be included in the lozenges composition

№	Raw materials and auxiliary materials	Technical requirements
1	Dried licorice extract	Quality standard (Academy of drug research 2020-3 -18)
2	Ginger powder	Chinese Pharmacopoeia 200 5, Vol.1 page 280-281
3	*Eugenia caryophyllata*powder	Chinese Pharmacopoeia 2005, Vol.1 page 87
4	Menthol	Chinese Pharmacopoeia 2005, Vol.1 page 87
5	Sugar	Chinese Pharmacopoeia 2005, Vol.1 page 87
6	Molasses	Quality standard (MonosPharna, GMP)

The selected raw materials must meet the technical requirements.

The following picture shows the technological scheme of lozenge manufacturing.



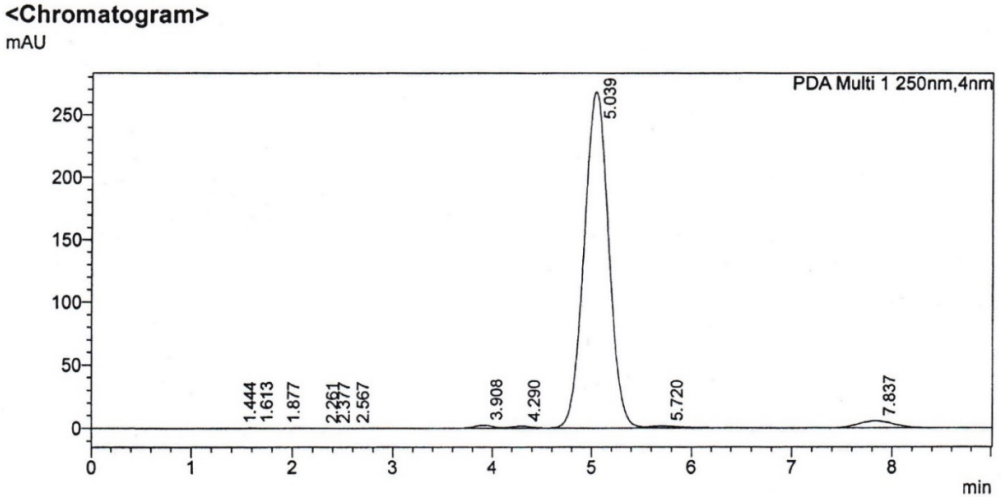
Picture1. Lozenge manufacturing technological scheme

We have prepared lozenges in accordance to the following technological steps of the scheme above:[5,10,15]

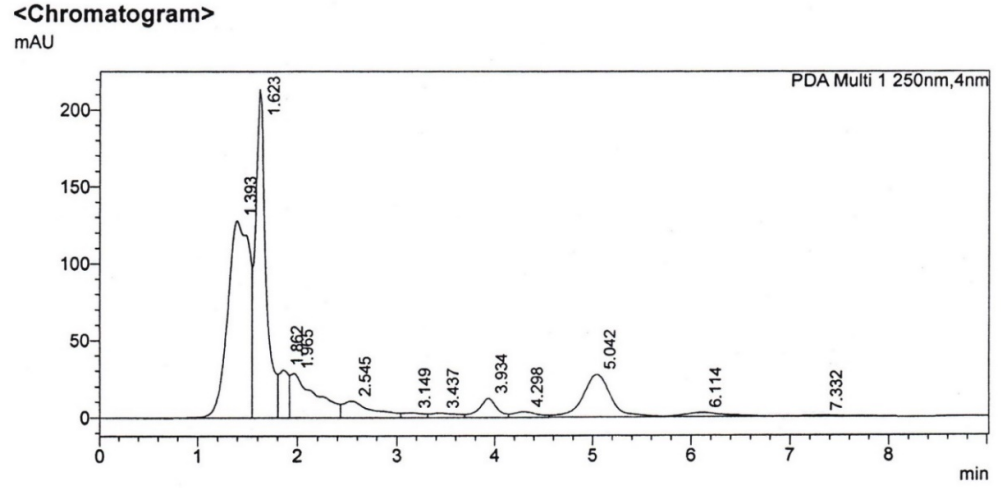
1. **Weighing and measuring the raw materials:** Measure and weigh the lozenge raw materials: clove, ginger and licorice, and lozenge base materials:sugar, molasses and concentrated sea buckthorn juice.
   1a. Grinding: Grind clove, licoriceand ginger finely into powder. (with mortar and pestle)
   1б. Sifting: Sift the powdered medicinal ingredient with sieve of 0.2 mm diameter.
2. **Preparing the base:** To prepare the base select a cooking pot, add 20 ml of distilled waterand bring to a boil. Then bring up the induction oven temperature to 150^0C, add 50 gr of sugar and mix well while it boils. After stirring thoroughly add 50 ml of molasses and 20 ml of concentrated sea buckthorn juice and mix well.
3. **Adding the raw medicinal ingredients:** Check the base temperature with thermometer. When it reaches 150^0C add the finely grounded raw ingredients, licorice, ginger and clove, and stir gently.Add a bit of menthol to the prepared mixture and stir until smooth.
4. **Measuring and pouring into a mold:** Pour the prepared mixture in molds of 2.5 gr.
5. **Cooling and refrigerating:**Cool lozenges for 20-30 minutes in room temperature of 15-20^0C.
6. Check the quality of lozenges and package.
7.

The result of some qualityindicatorsof the lozenge
Glycyrrhizinic acid content in the lozengesdeterminedwith high performance liquid chromatographymethod.

The following figures show the amount of the glycyrrhizinic acid content of the lozenges compared to pure glycyrrhizinic acid, a standard substance, determined with high performance liquid chromatography (HPLC) method.



Pcture2. High performance liquid chromatogram of the standard substance (glycyrrhizinic acid)



Picture3. High performance liquid chromatogram of the lozenges

(Chromatography conditions: Mobile phase-methanol:glacial acetic acid:0.2Mammonium acetate /67:1:33/, Column – C18, temperature-40℃, UV detector-250 nm,flow rate-1.2ml/min)

The glycyrrhizinic acid contentcontent per unit of product is calculated by the following formula, expressed in mg:

$$X=\frac{Sx*ast*V2*A\%}{Sst*V1*ax*100\%}*1000*P$$

Table6. Glycyrrhizinic acid content

Indicator	Glycyrrhizinic acid content of the dry extract of licorice (100 gr)	Glycyrrhizinic acid content of a lozenge(0.4 gr of licorice)	
		Ideal amount	Amount contained in the final product
Glycyrrhizinic acid	9.92 gr	39.6 mg	11.7 mg

As shown in the table above, with high performance liquid chromatography method we determined the glycyrrhizinic acid content contained in 100 gr of dry extract of licorice was 9.92 gr, and glycyrrhizinic acid content of one lozenge, which weighs 2.5 gr on average, was 11.7 mg.

The following table shows how some of the quality criteria of the lozenges are calculated according to the appropriate methodology and how they meet the requirements

Table7.A fewof the qualityindicator results of the lozenges

№	Standard indicators	Test sample (a lozenge)
1	Appearance (Sweet and sugary, brown, distinctive refreshing aroma)	match
2	Average weight, weight variation M=2.5*ср*	(n=5) M=2.5*ср* ±4%
3	Oral solubility Basic phosphate buffer solution (6.8-7.0) 10 min	match
4	Durability index (less than 97%)	(n=5) M=99.2±0.01% *
5	Moisture content (0.18%)	(n=5) M=0.18±0.01%*
		*p<0.05

From the table above, it can be seen that the appearance, base quality, solubility, average weight (n = 5) M = 2.5 ± 0.02 g, weight variation (± 4%) and durability index (n = 3) M = 99.2 ± 0.01% and moisture content (n = 5) M=0.18±0.01% p<0.05, are in appropriate range. This shows that the lozenges we have made meet the quality criteria.

Discussion

Researchers from India, Perumalla Jagadeesh and Arashad Ahamad, have developed a technology to prepare lozenges in three ways. First: Compressed tablet lozenges are prepared with dry and wet granulation methods. Second: Soft lozenges are prepared by pouring the melt into molds.Third: Hard candy lozenges: First step is to prepare candy base.Add corn syrup to the base and heat the base until it reaches 145-156^{0}C. Then add colorants, flavoringsand medicinal ingredients, and mix well. Afterwards measure and pourthe mixture in molds. [7,13]

We have completed the research in compliance with the technology to prepare hard candy lozenges.[16] The appropriate base cooking temperature in our research was 150^{0}C, which was in line with the temperature the research detailed.

We have developed technology of *Glycyrrhiza uralensis* Fisch lozenges with a 7-step scheme. It was in conformity with the research methods of researchers Perumalla Jagadeesh*, D. Arshad Ahammad, Suchitra Pundir* and Abhay Murari Lal. [5,6,17]

Some of the quality indicatorsof our lozenges, appearance, base quality, average weight (n = 5) M = 2.5 ± 0.02 g, weight variation (± 4%), strength (n = 5) M = 99.2 ± 0.01%, moisture content (n = 5) M = 0.18 ± 0.01% and * p <0.05 oral solubility of 10 minutes corresponds to the standard criteria of lozenges.

The content of glycyrrhizinic acid, a biologically active substance of dried licorice extract*(Glycyrrhiza uralensis* Fisch), determined with a high-performance liquid chromatography was 9.92 gr in 100gr of dried licorice extract and 11.7 mg in one lozenge. This result corresponds to 15 mg content of glycyrrhizinic acid found in imported lozenge Dr. Mom (Average weight of 2.5 g).

Conclusions

1. Developed technological scheme oflicorice extract lozenges with 7 principal steps including weighing and measuring of raw materials, grinding, sifting (siev, №8, diameter of 0.2mm), cooking the base (150^0C, 20-25 minutes), adding raw ingredients,mixing, stirring, measuring, pouring into molds, cooling and quality checking.
2. Determined the quality criteriaof the lozenges such as appearance, base quality, average weight (n = 5) M = 2.5 ± 0.02 g, weight variation (± 4%), strength (n = 5) M = 99.2 ± 0.01%, moisture content (n = 5) M = 0.18 ± 0.01% and * p <0.05 oral solubility of 10 minutes, and glycyrrhizinic acid content of the dry extract of licorice, which was 9.92 g, and the glycyrrhizinic acid content of one lozenge was 11.7 mg.

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