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Development and technological research of medicated lozenges for catarrhal and aphthous stomatits` symptoms relief

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Abstract: *inflammatory diseases of the oral cavity, in particular catarrhal and aphthous stomatitis, create significant discomfort for patients in everyday life. The occurrence of stomatitis in adolescents can be associated with numerous factors: bacterial and viral infection, insufficient oral hygiene, trauma of the mucous membrane, unbalanced nutrition, allergic reactions, some types of systemic diseases etc. Medicated lozenges have advantages for use in adolescents, as they have an interesting appearance (resembling a candy), pleasant taste and aroma, do not require swallowing or washing down with water, release active pharmaceutical ingredients by gradual dissolution in the oral cavity, which ensures their local action. The present work is aimed to develop different formulations of medicated lozenges for catarrhal and aphthous stomatits` symptoms relief. The objects of the study were experimental samples of lozenges with licorice root and propolis extracts. They were chosen as active ingredients due to their antimicrobial properties, as well as their ability to improve the general condition of the periodontium and reduce the outbreak of aphthae in stomatitis. Lozenges were prepared by heating and congealing method using different concentrations of active pharmaceutical ingredients and excipients (candy base substances – sugar substitute (isomalt), glucose syrup, carboxymethyl cellulose). 3 best formulations that had a uniform color distribution and were transparent, not sticky, had no external surface defects were subjects of the development and analysis. Obtained medicated lozenges were evaluated for physical parameters like weight variation, diameter and thickness, and pharmacotechnological evaluations like friability and hardness by pharmaceutical standard methods from State Pharmacopoeia of Ukraine 2.0 (2.9.5, 2.9.7, 2.9.8). Selected samples had homogeneous physical parameters: average weight in the range of 6.98-7.00 g (none of the formulations had a deviation of more than ± 5%), diameter 3.51 cm, thickness 5.04-5.11 mm. The obtained values of hardness and friability (less than 1% for all formulations) indicate satisfactory mechanical strength of the dosage form. Stability study was carried out at (15-25) ºC and 60±5 % humidity rate and was determined by evaluating the appearance and pharmacotechnological parameters. The values of hardness and friability were constant throughout the storage period for all formulations. Stability studies indicated that the formulations № 1 and 2 were stable for 30 days. The present research allowed to develop formulations for obtaining a pleasant-tasting dosage form intended for relatively slow dissolution in the oral cavity – medicated lozenges for use in adolescents to alleviate the symptoms of catarrhal and aphthous stomatitis.*

Key words: dosage forms, glycyrrhiza, oromucositis, licorice, stomatitis.

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Introduction

Inflammatory diseases of the oral cavity, in particular catarrhal and aphthous stomatitis, create significant discomfort for patients in everyday life. With untimely medical care and the use of self-treatment methods, the disease progresses and leads to the formation of significant and painful ulcers (aphthae) in the oral cavity, fever, general weakness, etc. Since the prevalence of the disease is extremely high (up to 25% of the population suffers from stomatitis) and has a high risk of recurrence (up to 50%), timely diagnosis and therapy are key in the treatment of this health status (Koberová et al., 2020). The occurrence of stomatitis in adolescents can be associated with numerous factors: bacterial and viral infection, insufficient oral hygiene, trauma of the mucous membrane, including in the case of improper selection of hygiene products (hard toothbrush, too large interdental bristles, improper brushing technique), unbalanced nutrition, allergic reactions, some types of systemic diseases (Hara et al., 2019, Koberová et al., 2020). As noted by Koberová et al. (2020), extremely important factors in the treatment of stomatitis in adolescents, in addition to drug treatment, are compliance with a special diet (non-traumatic for the oral mucosa) and thorough and gentle brushing of teeth and interdental spaces, which sometimes is impossible for adolescents to do on their own without the help and control of parents.

In order to ensure the required level of compliance, we chosed a solid form of hard candy lozenges group as a dosage form – lollipop. Medicated lozenges have advantages for use in adolescents, as they have an interesting appearance (resembling a candy), pleasant taste and aroma, do not require swallowing or washing down with water, release active pharmaceutical ingredients by gradual dissolution in the oral cavity, which ensures their local action, so they can be alternative dosage forms (Hordiienko & Nroshovyi, 2017, Pawar et al., 2018, Shetty et al., 2019, Hejaz et al., 2020, Sahoo et al., 2021). In addition, from a technological point of view, lozenges are quite simple to produce, process do not require special equipment and expensive excipients (Jagadeesh et al., 2017).

Classically, the basis of lozenges is a candy base (caramel), consisting of sugar or its substitutes. From the point of harmlessness to the oral cavity, isomalt is an alternative to sugar, because oral bacteria cannot convert it into polyglucan, from which, in turn, plaque is formed (Kini et al., 2011, Hordiienko & Nroshovyi, 2017).

The choice of formulation`s components was based on the analysis of scientific publications. It has been proven that licorice extract prevents the formation of caries, as it has an antimicrobial effect on *Streptococcus mutans* and *Lactobacillus acidophilus* (Messier et al., 2012, Almaz et al., 2017, Moritani et al., 2018, Chen et al., 2019, Rai et al., 2020). It is worth noting that excessive consumption of licorice can lead to high blood pressure, hypokalemia, swelling of the legs, bloating, headaches, and fatigue. Licorice also has estrogenic activity and can have an abortifacient effect, so it is contraindicated during pregnancy (Nazari et al., 2017, Al-Snafi, 2018, Sharifi-Rad et al., 2021). Preparations containing licorice extract are not recommended for children under 12 years of age. If the normal level of consumption is observed in adequate doses, licorice extract does not show or shows small amounts of adverse reactions (Al-Snafi, 2018). The European Food Safety Authority panel specify that licorice extract is safe up to 100 mg daily as a food additive (Sharifi-Rad et al., 2021). It is suggested that the acceptable daily dose of glycyrrhizin (as one of the main chemical components) is 0.015–0.229 mg/kg body weight/day (Isbrucker et al., 2006 as cited in El-Saber Batiha, 2020).

Propolis is able to inhibit the growth of bacteria in the oral cavity, improve the general condition of the periodontium and reduce the outbreaks of aphthae in stomatitis (Samet et al., 2007, Saeed et al., 2021). In combination, these components can reduce the impact of risk factors for the development of inflammatory diseases of the oral cavity and alleviate the symptoms of their mild manifestations.

Aim

To develop a formulation of medicated lozenges with licorice root extract and propolis oil extract by comparing the physical and pharmacotechnological parameters of experimental samples.

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Materials and methods

Such active pharmaceutical ingredients and excipients were used: licorice root extract (Zagros Licorice Co., Iran), propolis oil extract (Ingredient China Group Ltd., China), isomalt (Laped, Italy), glucose syrup (Laped, Italy), carboxymethyl cellulose FH 6000 (supplier «Ingredia» LLC, Ukraine), purified water, citron flavoring. Lozenges were prepared by heating and congealing method: the required amount of water, isomalt and glucose syrup was heated to a temperature of 160-170 ºC until the isomalt crystals were completely dissolved. The flavor was added at a reduced temperature to 120-130 ºC. Introduction of licorice root extract and propolis oil extract, carboxymethyl cellulose to the mixture was carried out at 80 ºC. The homogeneous mixture was poured into calibrated molds and left to congealing for 1 hour at room temperature 20±5 ºC. The obtained lozenges were subjected to various physical and pharmacotechnological evaluations immediately after congealing, and after 7 and 30 days storage period at (15-25) ºC temperature and 60±5 % humidity rate (formulations were wrapped in foil and storaged in a hermetically sealed polymer container). The pharmacotechnological parameters of the dosage form were determined. 20 lozenges were weighed on an electronic balance TBE-0.5-0.01 and the average weight and weight variation were calculated (the permissible deviation from the average should be not more than ± 5%). The diameter and thickness were measured for 10 lozenges with a Dnipro-M HP-15 caliper. Determination of friability was carried out on the PTF 10E single-drum tablet friability test instrument, Pharma test for 5 lozenges (permissible value – not more than 1%). 10 lozenges were subjected to the hardness test on PTB-M manual tablet hardness testing instrument, Pharma test (SPhU 2.9.5, 2.9.7, 2.9.8, Jagadeesh et al., 2017, Shetty et al., 2019).

Results

3 formulations formed visually the best lozenges after numerous experimental attempts (Table 1). They were subjects of the development and analysis. The obtained samples had a uniform color distribution, were transparent, not sticky, had no external surface defects.

Obtained medicated lozenges were evaluated for physical parameters like weight variation, diameter and thickness, and pharmacotechnological evaluations like friability and hardness by pharmaceutical standard methods from State Pharmacopoeia of Ukraine 2.0 (2.9.5, 2.9.7, 2.9.8) immediately after congealing and after 7 and 30 days storage period (Table 2). Selected samples had homogeneous physical parameters: average weight in the range of 6.98-7.00 g (none of the formulations had a deviation of more than ± 5%), diameter 3.51 cm, thickness 5.04-5.11 mm. The obtained values of hardness and friability (less than 1% for all formulations) indicate satisfactory mechanical strength of the dosage form. Stability study was carried out at 20±5 ºC temperature and 60±5 % humidity rate and was determined by evaluating the appearance and pharmacotechnological parameters. The values of hardness and friability were constant throughout the storage period for all formulations. Stability studies indicated that the formulations № 1 and 2 were stable for 30 days.

Table 1. Formulation table of licorice root extract and propolis oil extract medicated lozenges

Ingredients (%)	Formulation №1	Formulation №2	Formulation №3
Licorice root extract	1,5	1,5	1,5
Propolis oil extract	1,5	1,5	1,5
Isomalt	80	80	80
Glucose syrup	-	2	1
Carboxymethyl cellulose	1	-	1
«Citron» flavour	1 drop	1 drop	1 drop
Purified water	16	15	15

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Table 2. Physical and pharmacotechnological evaluations of lozenges formulations after congealing and during stability studies

Evaluation	Formulation №1	Formulation №2	Formulation №3
Storage period - 0 days			
Appearance	Light yellow transparent lozenges, uniform in shape, without external surface defects, sometimes with air bubbles		
Weight Variation (gm)±SD	7,00±0,06	6,98±0,07	6,99±0,08
Diameter (cm)	3,510±0,010	3,510±0,008	3,510±0,008
Thickness (mm)	5,11±0,04	5,04±0,05	5,04±0,06
Friability (%)	0,52	0,38	0,43
Hardness (N/ cm2)	92,58±0,05	73,62±0,27	73,66±0,24
Storage period - 7 days (stability studies)			
Appearance	Unchanged		Sticky and shiny surface
Friability (%)	0,54	0,46	0,49
Hardness (N/cm2)	92,64±0,11	73,71±0,19	73,85±0,26
Storage period - 30 days (stability studies)			
Appearance	Unchanged		Sticky and shiny surface
Friability (%)	0,54	0,49	0,49
Hardness (N/cm2)	92,69±0,08	73,78±0,22	73,97±0,25

Discussion

There are few publications of design and development lozenges` various formulations with herbal ingredients. Hu et al. (2011) developed a sugar-free candy formulation with licorice root extract using a mixture of starch hydrolysate and acesulfame potassium (as a candy base), flavors and colors. The use of this sweetener raises some questions, because acesulfame potassium is a substance that is regulated in European consumption standards – it can`t be used in food processing industry in the European Union (Commission regulation (EU) 2018/97, 2018). Bane et al. (2022) formulated a candy base of lozenges with *Emblica officinalis* extract with a mixture of isomalt and mannitol.

Technologically, the manufacturing process consisted of 3 main stages: preparation of the candy base (caramel), the introduction of active ingredients and the formation of lozenges. All these stages caused certain difficulties in implementation. For example, the slightest deviation from the optimum temperature led to unsatisfactory performance, the caramel formed a viscous mass that did not congeal. Increasing or decreasing the percentage of both the sum of active ingredients and water affected the hardness and quality of the formed candy structure, some experimental samples melted in the hands (at body temperature). The ratio of the content of isomalt, glucose syrup and carboxymethyl cellulose had an influence on the hardness of the obtained dosage forms as well. It should be noted that the primary obtaining of the hard candy structure of the candy base with active ingredients immediately after congealing does not guarantee the preservation of the structure during storage period. The lozenges with a mixture of carboxymethyl cellulose and glucose syrup (formulation № 3) formed a solid solution and congealed in a certain period of time, but during storage the lozenges became sticky, liquid drops appeared on the surface. That indicates a high level of formulation hygroscopicity. Formulation № 1 formed a thick consistency, which formed a very hard candy structure. The presence of carboxymethyl cellulose prolongs the action of the lozenges in the oral cavity due to high hardness and increased dissolution time of the dosage form. Formulation № 2 containing 80% isomalt and 2% glucose syrup formed a classic caramel structure, which congealed within 1 hour, forming a lozenge of a certain shape that did not

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change its structure during the storage period. In the process of resorption, the lozenges did not lose their shape (did not disintegrate) and did not stick to the teeth. The proposed formulations № 1 and № 2 allow to form medicated lozenges of pleasant taste, moderate sweetness, sufficient or high hardness and stability. Further studies on the release of active ingredients are necessary.

Conclusions

The present research allowed to develop formulations for obtaining a pleasant-tasting dosage form intended for relatively slow dissolution in the oral cavity – medicated lozenges for use in adolescents to alleviate the symptoms of catarrhal and aphthous stomatitis.

Financing

This study did not obtain any external funding or financial support.

Conflict of interests

Authors have no conflict of interest to declare.

Consent to publication

All authors have read and approved the final version of this manuscript. All authors agreed to publish this manuscript.

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Розробка та технологічне дослідження льодяників для полегшення симптомів катарального та афтозного стоматитів

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Анотація: запальні захворювання ротової порожнини, зокрема катаральний та афтозний стоматити створюють значний дискомфорт для пацієнтів у повсякденному житті. Поява стоматитів у підлітків може бути пов'язаною із численними факторами: бактеріальною та вірусною інфекцією, недостатньою гігієною ротової порожнини, травмуванням слизової оболонки, в тому числі при неправильному підборі засобів гігієни, незбалансоване харчування, алергічна реакція, деякі види системних захворювань. Льодяники володіють перевагами для застосування у підлітковому віці, оскільки мають цікавий зовнішній вигляд (нагадують цукерку), приємний смак та аромат, не потребують ковтання чи запивання водою, вивільняють активні фармацевтичні інгредієнти при поступовому розчиненні у ротовій порожнині, що забезпечує їхню місцеву дію, тому можуть бути альтернативними лікарськими формами. Метою дослідження було розробити рецептуру льодяників для полегшення симптомів катарального та афтозного стоматитів. Об'єктами дослідження були експериментальні зразки льодяників із екстрактами солодки кореня та прополісу. Їх було обрано активними інгредієнтами зважаючи на антимікробні властивості, а також здатність покращувати загальний стан пародонту та зменшувати

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спалахи афт при стоматиті. Для одержання льодяників використовували метод нагрівання та застигання різних концентрацій активних інгредієнтів та допоміжних речовин (складових цукеркової основи – замінника цукру (ізомальту), глюкозного сиропу, карбоксиметилцелюлози). Візуально найкращі льодяники формували 3 рецептури, які в подальшому і підлягали напрацюванню та аналізу. Одержані зразки мали рівномірний розподіл кольору, були прозорими, не липкими, не мали зовнішніх дефектів поверхні. Проводили визначення фізичних показників (середня маса та однорідність маси, діаметр та товщина) та фармакотехнологічних параметрів (стиранність та стійкість до роздавлювання) одержаних льодяників відповідно методик Державної фармакопеї України 2.0 (2.9.5, 2.9.7, 2.9.8). Відібрані зразки мали однорідні фізичні параметри: середню масу у межах 6,98-7,00 г (жоден із зразків не мав відхилення більше допустимого ±5 %), діаметр 3,51 см, товщину 5,04-5,11 мм. Одержані значення стійкості до роздавлювання та стиранності (менше 1 % для усіх експериментальних зразків) свідчать про задовільну механічну міцність лікарської форми. Стабільність льодяників визначали оцінюючи зовнішній вигляд та технологічні показники після зберігання при температурі (15-25) ºС та вологості 60±5 %. Значення стираності і стійкості до роздавлювання були сталими протягом усього терміну спостереження для усіх експериментальних зразків. Дослідження стабільності показали, що експериментальні зразки № 1 та 2 були стабільними протягом 30 днів. Наявне дослідження дозволило сформувати рецептури для одержання приємної на смак лікарської форми, призначеної для відносно повільного розчинення у порожнині рота –льодяників для застосування дітям та підліткам з метою полегшення симптомів катарального та афтозного стоматитів.

Ключові слова: лікарська форма, солодка, льодяники, прополіс, стоматит.