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# Development of the composition and technology of an orodispersible film with melatonin and magnesium citrate

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***Abstract:*** *sleep disorders are one of the most common problems among the population today. Numerous scientific publications indicate the effectiveness and safety of melatonin and magnesium use as active ingredients in medicinal products in older adults with sleep disorders. The technological development of an oromucosal preparation – an orodispersible film with melatonin and magnesium citrate is relevant in view of the possibility of increasing the patients' compliance, those who find it difficult to take oral dosage forms (tablets, capsules) due to possible hand tremors and swallowing disorders. The aim of the study was to develop orodispersible films' with melatonin and magnesium citrate formulations of various compositions, to conduct a comparative study of their technological parameters in order to select the optimal composition of excipients. The orodispersible films were made by solvent casting method. Melatonin and magnesium citrate were combined with representa-tives of 6 excipients groups (hydrophilic polymers: agar-agar, xanthan gum, sodium alginate, carbox-ymethyl cellulose, hydroxy-propyl methyl cellulose E3, plasticisers: macrogol 400, glycerol and pro-pylene glycol, saliva stimulants: ascorbic, lactic and citric acids, disintegrant: sodium croscarmellose, sweeteners: sorbitol, erythrol and sucralose, solvent: purified water). Formulations of 9 experimental samples were formed. The prepared solutions were filled into appropriate Petri dishes and dried in several steps. The technological parameters of the dried and cut into 2×3.5 cm orodispersible films were determined: appearance and surface characteristics, average weight and it`s uniformity, area and film thickness, folding endurance, in-vitro disintegration time, and physico-chemical parameter: surface pH value. Formulation No. 5, when dried at 60 ºC for 3 hours and 60 ºC for 3 hours / 40 ºC for 2 hours, and left for congealing for 24 hours at 25 ± 2 ºC, formed dry to the touch, durable elas-tic transparent orodispersible film with very close stable values of parameters (average weight 0.40 ± 0.01 g, area 7 cm², thickness 0.32 ± 0.05 mm and 0.32 ± 0.03 mm, respectively, folding endurance > 300, pH 6.70 ± 0.04 and 6.74 ± 0.05, respectively, in-vitro disintegration time 32.00 ± 0.67 s and 31.00 ± 0.67 s, respectively). The technology is suitable and it is possible to obtain dry to the touch, durable, elastic transparent films with satisfactory values of the studied parameters under the speci-fied drying conditions.*

**Keywords:** dosage forms, magnesium, melatonin, sleep initiation and maintenance disorders, technology.

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## Introduction

Sleep disorders are one of the most common problems among the population today, especially in older adults. Very often, insomnia is the cause of deterioration in physical and mental health: fatigue, reduced attention, irritability, depression, etc. Sleep deprivation and poor sleep quality are risk factors for obesity, diabetes, cardiovascular diseases (Xie et al., 2017). According to various data, the prevalence of sleep disorders among adults ranges from 10-15% (Winkelman, 2015) to 30-50% (Tuft et al., 2023), and among patients of neurological practice 40-83%, depending on the form of the underlying pathological state (Kyrylova et al., 2021). It is also known that sleep disorders are one of the key features of neurodegenerative diseases: they are observed in 70% of patients with early dementia and 86% of patients with Parkinson's disease (Tuft et al., 2023).

The treatment of insomnia mild forms primarily consists of the so-called «sleep hygiene». The use of drug therapy is necessary in the treatment of insomnia moderate and severe forms. Group of prescription medicines (sedatives, antidepressants, hypnotics, etc), are used in most cases. They often cause undesirable side effects (dizziness, headache, nausea, daytime sleepiness, and addiction) (Kopchak, 2019).

Melatonin is a pineal hormone that has antioxidant properties. Melatonin regulates circadian rhythm (improves total sleep duration), it is an endogenous sleep inducer (Low et al., 2020). Melatonin can be synthesised only at night when there is no light (Tordjman et al., 2017, Xie et al., 2017). Ageing is associated with a decrease in melatonin production and an increase in sleep disorders in older adults. This has led to the «melatonin replacement» hypothesis, which predicts that exogenous hormone replacement therapy will improve sleep/wake periods. Achieving physiological control of sleep is the goal of replacement therapy in patients with sleep disorders aged 55 years and older, because this group has low endogenous melatonin production during the night (Pierce et al., 2019). Numerous publications indicate that melatonin is used to treat age-related insomnia (Cardinali et al., 2012, Xie et al., 2017, Palagini et al., 2021, Schroder et al., 2021, Marupuru et al., 2022, Tuft et al., 2023).

Literature data recommends a wide range of melatonin doses (from 0.5 mg to 10 mg) and it's taking 1 hour before sleep (Vural et al., 2014, Tuft et al., 2023). 2 mg melatonin dose was used in many studies involving older adults with insomnia. The maximum concentrations reached by exogenous melatonin were higher in older adults than in younger patients. High doses can lead to prolonged supraphysiological melatonin levels in the blood and possible side effects. In general, 1 mg to 6 mg melatonin doses appear to be effective in improving sleep in older adults (Pierce et al., 2019).

Placebo-controlled clinical trials with melatonin in patients aged 55 years and older have demonstrated that melatonin improves sleep quality, reduces sleep latency, increases morning energy. Studies show that melatonin does not cause withdrawal symptoms and is safe for use in older adults, even in the presence of the most common comorbidities (e.g., hypertension, diabetes, angina) (Pierce et al., 2019).

Melatonin preparations can be registered only as dietary supplements in USA, non-prescription or prescription medicines, and dietary supplements in most countries of the European Union and Australia, and medicines available only on prescription in Great Britain (Tuft et al., 2023).

The use of magnesium in patients with sleep disorders is attributed to the promotion of normal muscle function, including muscle relaxation. The required concentration of the element in the human body helps to counteract stress, tension, anxiety and depression (Davtyan et al., 2022). Magnesium is a gamma-aminobutyric acid agonist, which leads to calming of nervous activity and increase melatonin levels, thereby contributing to the normalisation of sleep. Magnesium intake improves sleep efficiency, sleep duration, and early morning awakening (Abbasi et al., 2012).

The technological development of oromucosal medicines – orodispersible films with melatonin and magnesium citrate is relevant due to the possibility of increasing the patients' compliance in older adults, who find it difficult to take oral dosage forms (tablets, capsules) due to possible hand tremors and dysphagia, as swallowing disorders are common complication of most neurological diseases that are typical for older adults (Pimparade et al, 2017).

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**Aim**

To develop formulations of orodispersible films with melatonin and magnesium citrate different compositions, to conduct a comparative study of their technological parameters in order to select the optimal excipients.

**Materials and methods**

Melatonin (Sigma-Aldrich Co, USA), magnesium citrate (Now Foods, USA), agar-agar (Kremer Pigmente GmbH & Co. KG, Germany), Cosphaderm® X 34 – xanthan gum (Cosphatec GmbH, Germany), sodium alginate (Landor Trading Company, China), carboxymethyl cellulose (Fufeng Group, China), hydroxypropyl methyl cellulose E3 (JRS PHARMA GmbH & Co. KG, Germany), Macrogol 400 (BASF, Germany), glycerol (supplied by «Sfera Sim», Ukraine), propylene glycol (supplied by «Sfera Sim», Ukraine), sodium croscarmellose (JRS Pharma & GUJARAT MICROWAX Pvt, Ltd., India), ascorbic acid (Foodchem International Corporation, China), lactic acid (supplied by Klebrig TM, Ukraine, manufactured in France), citric acid (Seven Star Lemon Technology Co., Ltd., China), sorbitol (Hugestone Enterprise Co., Ltd., China), erythritol (Ingredion UK Limited, UK), sucralose (Shandong Kanbo Biochemical Technology Co., Ltd., China) were used.

The area of the Petri dish' inner surface and the area of one orodispersible film were determined. The required amount of active pharmaceutical ingredients (APIs) was calculated to ensure the content of melatonin 2 mg and magnesium citrate 20 mg in one film.

Orodispersible films were made by solvent casting method: the required amount of purified water was heated to a temperature of 60 ºC. Purified water was divided into 2 equal parts. The required amount of hydrophilic polymer was dissolved in the first part. The required amount of melatonin was dissolved in the second part of the purified water. Both solutions were prepared under constant stirring with a magnetic stirrer. Magnesium citrate, saliva stimulant, disintegrant, sweetener, and plasticiser were added after the formation of a clear melatonin solution. Two solutions were mixed together in a separate container and stirred for 5 minutes. The mixture was poured into containers and left for 24 hours to remove trapped air that appeared during the preparation of formulation. The solution was poured into a suitable Petri dish and dried.

Drying was carried out by thermal method at temperature of 60 ºC for 3 hours (left to congealing for 24 hours at room temperature of 25 ± 2 ºC). 2 more drying methods were also tested for individual formulations during the study: thermal drying at 80 ºC for 2 hours (left to congealing for 24 hours at 25 ± 2 ºC); thermal drying at 60 ºC for 3 hours, 40 ºC for 2 hours (left to congealing for 24 hours at 25 ± 2 ºC).

The technological parameters of the dried and cut into 2×3.5 cm orodispersible films were determined: appearance and surface characteristics, average weight and it's uniformity (electronic balance TBE-0.5-0.01), area and film thickness (Dnipro-M HP-15 caliper and SK200 thickness tester), folding endurance, *in-vitro* disintegration time (Petri dish method), and physico-chemical parameter: surface pH value (universal ionometer EV-74) (Mahmod & Khalil, 2015, Bonsu et al., 2016, Tamer et al., 2018, Popovici et al., 2022).

**Results and discussion**

Orodispersible films obtaining depends on the name and amount of excipients, physical and chemical properties of APIs, certain critical stages of manufacturing process: solvent temperature, the order of APIs and excipients introduction into solution, stirring speed, drying parameters (temperature and duration of process). Characteristics of drying process have the significant impact on medicinal product structure formation – from solution to gel mass, from solution to elastic film, from solution to dry brittle film.

The excipients were selected based on recommended lists, that are available in scientific publications (Davtyan & Holod, 2013, Irfan et al., 2016, Joshua et al., 2016, Demchuk et al., 2017, Özakar & Özakar, 2021, Demchuk et al., 2022). Agar-agar, xanthan gum, sodium alginate, carboxymethyl cellulose and hydroxypropyl methyl cellulose E3 were used as hydrophilic polymers. Macrogol 400, glycerol and propylene glycol were used as plasticisers. Sodium croscarmellose acted as a superdisintegrant. Ascorbic, lactic, and citric acids were used as stimulants of saliva formation. Sorbitol, erythritol and sucralose were used as sweeteners. Purified water was a solvent. Melatonin and magnesium citrate were combined with representatives of 6 excipients groups. Formulations of 9 experimental samples were formed (table 1). The pre-

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pared solutions were poured into appropriate Petri dishes and dried in several steps.

The mass sticking to the surface of Petri dish and films' non-uniformity with a large number of air bubbles and gaps (holes) was observed for formulations No. 1 and No. 2 after drying at 60 ºC for 3 hours (congealing within 24 hours at 25 ± 2 ºC). The films became yellow in colour. Repeated preparation and drying at 80 °C for 2 hours (congealing within 24 hours at 25 ± 2 ºC), and at 60 °C for 3 hours and 40 °C for 2 hours (congealing within 24 hours at 25 ± 2 ºC) were performed for these formulations. In first case, adhered to the surface film was formed, in second case, an elastic film was formed, but yellowing of the mass was also observed, that is unacceptable. Formulation No. 3 was more successful, had an uniform surface, and was translucent with a small number of air bubbles, but the film was dry and not plastic. This can be explained by the lack of plasticisers, as they provide elasticity of the mass and reduce the fragility of the dosage form. Formulations No. 6–8 did not congeal and were sticky to the touch. An additional study was also conducted using two more drying parameters for these formulations. Formulations No. 4, No. 5 and No. 9 were most successful. They formed a plastic film. Formulations were cut into 2×3.5 cm films and their technological parameters were determined: appearance and surface characteristics, average weight and it's uniformity, area and film thickness, folding endurance, *in-vitro* disintegration time, and physico-chemical parameter: surface pH value (table 2). The obtained films were transparent (formulations No. 4 and No. 5), elastic, dry to the touch, sometimes with air bubbles. Formulation No. 9 had an inhomogeneous white colour, but was dry and elastic.

Formulation No. 9 was excluded from the further experiment, since significant deviations were observed in different measurement angles (from 0.2 to 0.6 mm) when determining the film thickness, i.e. the film surface was not smooth and contained thickenings in some places. Orodispersible films had an average weight in the range of 0.39–0.42 g, thickness in the range of 0.28-0.4 mm, and a surface pH value in the range of 6.42–6.82. The

**Table 1.** Formulation table of melatonin and magnesium citrate orodispersible films

| Ingredients | Formulations | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Melatonin, mg | 20,24 | 20,24 | 20,24 | 20,24 | 20,24 | 20,24 | 20,24 | 20,24 | 20,24 |
| Magnesium citrate, g | 3,036 | 3,036 | 3,036 | 3,036 | 3,036 | 3,036 | 3,036 | 3,036 | 3,036 |
| Agar-agar, g | 0,2 | | | | | 0,1 | | | |
| Xanthan gum, g | | 0,2 | | | | 0,1 | | | 0,1 |
| Sodium alginate, g | | | 0,2 | | | | 0,1 | 0,1 | |
| Carboxymethyl cellulose, g | | | | 0,2 | | | | 0,1 | |
| Hydroxypropyl methyl cellulose E3, g | | | | | 0,2 | | 0,1 | | 0,1 |
| Macrogol 400, g | 1,0 | | | 2,0 | | | 3,0 | | |
| Glycerol, g | | 1,0 | | | 2,0 | | | 3,0 | |
| Propylene glycol, g | | | 1,0 | | | 2,0 | | | 3,0 |
| Ascorbic acid, g | 0,2 | | | 0,2 | | | 0,2 | | |
| Milk content, g | | 0,2 | | | 0,2 | | | 0,2 | |
| Citric acid, g | | | 0,2 | | | 0,2 | | | 0,2 |
| Sodium croscarmellose, g | 0,4 | 0,4 | 0,4 | 0,4 | 0,4 | 0,4 | 0,4 | 0,4 | 0,4 |
| Sorbitol, g | 0,5 | | | 0,5 | | | 0,5 | | |
| Erythrol, g | | 0,5 | | | 0,5 | | | 0,5 | |
| Sucralose, g | | | 0,1 | | | 0,1 | | | 0,1 |
| Purified water, g | 40,0 | 40,0 | 40,0 | 40,0 | 40,0 | 40,0 | 40,0 | 40,0 | 40,0 |

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**Table 2.** Physico-chemical and technological evaluations of an orodispersible films with melatonin and magnesium citrate formulations

| Evaluation | Formulation No.4 | Formulation No. 5 | Formulation No. 9 |
|---|---|---|---|
| Average weight and it's uniformity (g ± SD, n = 10) | 0,39 ± 0,02 | 0,40 ± 0,01 | 0,42 ± 0,01 |
| Area ($cm^2$, n = 10) | 7 | 7 | 7 |
| Thickness (mm ± SD, n = 10) | 0,28 ± 0,03 | 0,30 ± 0,04 | 0,4 ± 0,8 |
| Folding endurance (n = 5) | > 300 | > 300 | > 300 |
| pH (± SD, n = 5) | 6,42 ± 0,60 | 6,72 ± 0,06 | 6,82 ± 0,10 |
| Disintegration *in-vitro* (s ± SD, n = 3) | 48,33 ± 0,44 | 32,67 ± 0,44 | 40,00 ± 0,67 |

folding endurance value of more than 300 indicates sufficient strength and good flexibility (elasticity) of the formulations (Mahmod & Khalil, 2015).

Formulations showed a wide range of *in-vitro* disintegration test values. Formulation No. 5 disintegrated the fastest (mean value 32.67 s). Formulation No. 4 disintegrated the longest (mean value 48.33 s). Formulation No. 4 was excluded from further study because the disintegration rate of the drug is one of the most important pharmaco-technological characteristic for oromucosal drugs, responsible for the rate of release (dissolution) of APIs in biological fluid (saliva), as well as for ease of use, i.e. the level of patient compliance.

The next step was to determine the optimal drying temperature by comparing the formulations obtained under three different drying parameters (different temperature conditions and duration). All formulations after drying were stored at room temperature 25 ± 2 ºC wrapped in aluminium foil and placed in a hermetically sealed container. The test results are shown in the table 3.

Formulation No. 5, which was dried at 80 °C for 2 hours and congealed at 25 ± 2 °C for 24 hours, had a lower folding endurance (< 300), that indicates insufficient strength, elasticity of the dosage form, and its ability to brittle. Dry to the touch, strong, elastic transparent films with very close stable values of technological parameters were obtained when dried at 60 °C for 3 hours and 60 °C for 3 hours / 40 °C for 2 hours, and congealed for 24 hours at 25 ± 2 °C.

**Conclusions**

This experimental study allowed us to select excipients for the production of orodispersible films with melatonin and magnesium citrate (hydroxypropyl methyl cellulose E3, glycerol, lactic acid, sodium croscarmellose, erythrol, purified water). The determined physico-chemical (surface pH value) and pharmaco-technological (appearance and surface characteristics, average weight and it's uniformity, area and film thickness, folding endurance, *in-vitro* disintegration time) quality indicators of the developed films

**Table 3.** Technological evaluations of an orodispersible films formulation No. 5 under different drying parameters

| Evaluation / drying parameters | 60 ºC 3 hours / 25 ± 2 ºC 24 hours | 80 ºC 2 hours / 25 ± 2 ºC 24 hours | 60 ºC 3 hours / 40 ºC 2 hours / 25 ± 2 ºC 24 hours |
|---|---|---|---|
| Average weight and it's uniformity (g ± SD, n = 10) | 0,40 ± 0,01 | 0,37 ± 0,02 | 0,40 ± 0,01 |
| Area ($cm^2$, n = 10) | 7 | 7 | 7 |
| Thickness (mm ± SD, n = 10) | 0,32 ± 0,05 | 0,30 ± 0,08 | 0,32 ± 0,03 |
| Folding endurance (n = 5) | > 300 | 162 ± 18 | > 300 |
| pH ( ± SD, n = 5) | 6,70 ± 0,04 | 6,68 ± 0,06 | 6,74 ± 0,05 |
| Disintegration *in-vitro* (s ± SD, n = 3) | 32,00 ± 0,67 | 37,00 ± 0,67 | 31,00 ± 0,67 |

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allow us to conclude that the technology is suitable and it is possible to obtain dry to the touch, durable, elastic transparent films with satisfactory values of the studied parameters under the specified drying conditions. The study of the degree of active pharmaceutical ingredients release from the dosage form is an area for further research.

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**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 складу та технології плівки, що диспергується в ротовій порожнині з мелатоніном та магнію цитратом

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***Анотація:*** *у реаліях сьогодення порушення сну є однією із найбільш розповсюджених проблем серед населення. Численні наукові публікації вказують на ефективність та безпечність використання мелатоніну та магнію як активних інгредієнтів у складі лікарських засобів для застосування у пацієнтів похилого та старечого віку, що мають порушення сну. Технологічна розробка оромукозного лікарського засобу – плівки, що диспергується у ротовій порожнині з мелатоніном та магнію цитратом є актуальною зважаючи на можливість збільшення комплаєнсу пацієнтів, яким важко приймати пероральні лікарські форми (таблетки, капсули) через можливий тремор рук та та дисфагію, адже порушення ковтання є досить поширеним ускладненням більшості неврологічних захворювань, що характерні для геріатричних хворих.*

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*Метою роботи було розробити експериментальні зразки різних складів плівок, що диспергуються у ротовій порожнині з мелатоніном та магнію цитратом, провести порівняльне дослідження їхніх фармако-технологічних параметрів з метою вибору оптимального складу допоміжних речовин. Плівки виготовляли методом лиття розчинника. Мелатонін і магнію цитрат поєднували з представниками 6 груп допоміжних речовин (гідрофільні полімери: агар-агар, ксантанова камедь, натрію альгінат, карбоксиметилцелюлоза, гідроксипропілметилцелюлоза Е3, пластифікатори: макрогол 400, гліцерин та пропіленгліколь, стимулятори слиноутворення: аскорбінова, молочна та лимонна кислоти, розпушувач: натрій кроскармелоза, підсолоджувачі: сорбітол, еритрол та сукралоза, розчинник: вода очищена), та формували рецептури 9 експериментальних зразків. Приготовані розчини виливали у відповідні чашки Петрі та сушили у декілька прийомів. Проводили визначення фармако-технологічних параметрів висушеної та нарізаної на плівки розміром 2х3,5 см лікарської форми: зовнішній вигляд та характеристика поверхні, середня маса та відхилення від неї, площа та товщина, стійкість до згинання, розпадання in-vitro, та фізико-хімічних: значення pH. Експериментальні зразки № 5 при висушуванні за температури 60 ºС протягом 3 год та 60 ºС протягом 3 год / 40 ºС протягом 2 год, і наступного застигання протягом 24 годин за температури 25 ± 2 ºС формували сухі на дотик, міцні, еластичні прозорі плівки із дуже близькими стабільними значеннями фармако-технологічних параметрів (середня маса 0,40 ± 0,01 г, площа 7 см$^2$, товщина 0,32 ± 0,05 та 0,32 ± 0,03 мм відповідно, стійкість до згинання > 300, pH 6,70 ± 0,04 та 6,74 ± 0,05 відповідно, розпадання in-vitro 32,00 ± 0,67 та 31,00 ± 0,67 с відповідно). Технологія придатна для одержання сухих на дотик, міцних, еластичних прозорих плівок із задовільними значеннями досліджуваних параметрів за визначених умов сушіння.*

**Ключові слова:** лікарські форми, магній, мелатонін, порушення ініціації та підтримки сну, технологія.