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MODELING OF EXTEMPORANEOUS ORAL SUSPENSIONS FROM NYSTATIN TABLETS

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Abstract. In geriatrics and pediatrics, the production of extemporary liquid and solid drugs of individualized concentration from tablets is important in order to facilitate the use of medicines by patients, i.e. facilitate the dosage, method of administration, mask the unpleasant taste and smell of the medicinal substance with the help of auxiliary substances. Industrial production liquid suspensions with nystatin as an active substance for the treatment of symptoms of fungal infections and candidiasis are not registered in the Register of Medicinal Products in Lithuania. They can only be purchased for extemporal production. Therefore, it is relevant to look for ways to model modern, attractive for the patient to take a liquid drug from nystatin tablets, the need for which has remained for the treatment and improvement of candidiasis and other fungal infectious conditions. For this it is necessary to apply auxiliary substances.
Research methodology: Suspensions from nystatin tablets are produced by the method of mechanical dispersing. Suspensions are produced by the mass - volume method, applying the methodology for the production of suspensions of hydrophobic substances.
The quality of extemporal modeled drugs was evaluated after the following studies: the rate and extent of sedimentation; resuspending; organoleptic properties.
The results of the study. To stabilize extemporal medicinal suspensions with nystatin, it is recommended to use a 1% solution of hypromellose during production. When using this solution, the sedimentation of the suspension is very slow, so it is possible to accurately dose the medicinal substance. Modeled oral suspensions of extemporal production with nystatin from tablets met the applicable quality requirements, production schemes can be applied for extemporaneous production in pharmacies.
Keywords: extemporal, nystatine, suspension, sedimentation, hypromellose

Introduction

Medicinal liquid suspensions are usually called dispersions, in which the medicinal substance is a dispersed solid state in a liquid medium (carrier). Disperse phase – the diameter of the particles of the suspension can vary from about 0.5 to 100 μm. These suspensions are liquid heterogeneous systems, therefore they are characterized by aggregate and kinematic instability. Both in the production process and during storage, the dispersive phase occurs, can aggregate, sedimentate (Neha et al. 2022). Therefore, modeling such a pharmaceutical form to provide a medicinal substance with the task of stabilization and stability control arises. The pharmaceutical suspension would be considered stable if, after mixing /shaking, the particles of the drug are homogeneously distributed over a sufficiently long period of time to ensure that the patient is given an accurate dose (Costa et al. 2020). The acceptable pharmaceutical properties of the suspension are as follows: low sedimentation rate, the disperse phase should be easily distributed by gentle shaking, due to the flow properties of the suspension, the preparation should be easily removed from the container, sensory properties (El Mershati et al. 2021).

Suspensions are one of the most important forms of pharmaceutical dosages, which are widely used for hard-to-dissolve medicinal substances. They can be of different therapeutic purposes: for external, parenteral, ear, ophthalmic and peroral administration. Medicinal suspensions are produced in order to increase the stability of the drug when the medicinal substance is not soluble or poorly, to mask the unacceptable sensory properties of the medicinal substance, to prolong the action of the drug (Gaikwad et al. 2024). Orally administered pharmacy suspensions are liquid drugs for oral administration, a monodose or multidose preparation consisting of an active substance distributed in a liquid medium (Rahić et al. 2022). Each dose from a multidose container is measured with a volume meter – a teaspoon, a measuring cup. The most commonly used are 5 ml or their multiples (Neves, Auxtero, 2021). In their composition there may be excipients: stabilizers, antimicrobial preservatives, antioxidants, corrigents.

Requirements for medicinal suspensions: uniformity of the contents, volume of sediment, particle size, acceptable organoleptic properties, resuspending, fluidity - the suspensions should not be too viscous to be easily poured out of the container; have microbiological and chemical stability (Alfagih et al. 2023). The release of the medicinal substance, its speed and extent must remain the same throughout the shelf life of the suspension. Homogeneity is very important when dosing oral suspensions, so that with each simultaneous use, the patient should receive an equal dose of the medicinal substance (Rahman et al. 2021).

Extemporaneous production provides an opportunity to apply dosages or concentrations and the form of the drug acceptable in pediatrics or geriatrics. Most of the approved oral drugs for adults are available in the

form of tablets or capsules. However, the size of the dosage of drugs for children or elderly patients should be proportional to the surface area of the body and body weight - that is, individually calculated or adapted to a particular patient. In addition, most children and geriatric patients may have problems with swallowing for various reasons - they cannot swallow tablets, capsules, so extemporally made drugs can be the way out, for example, in the manufacture of liquid viscous suspensions from commercial drug tablets with acceptable organoleptic properties: taste, smell and consistency (Belayneh, Tessema, 2021).

Nystatin (Sklen et al. 2013) is an antifungal medicinal substance that is effective against *Candida, Cryptococcus, Aspergillus, Histoplasma and Blastomyces*. It is indicated for the treatment of oral candidiasis and fungal diseases of the pharynx, esophagus, stomach, is important for the prevention of oral and systemic candidiasis in newborns, infants and immunocompromised patients (Baldino et al. 2021). Oral candidiasis is a disease of the oral mucosa caused by fungi of the yeast genus, usually *Candida albicans*. *Candida albicans* is a yeast that, like baker's yeast, intersects in a moist and warm (35°C) medium, usually mucous membranes, skin, especially intestines. Symptoms: stinging in the mouth; feeling of a foreign body in the mouth; redness of the mucous membranes; white plaque on the mucous membranes; unpleasant smell from the mouth; dry mouth; mouth ulcers (Vila et al. 2020). For the treatment of candidiasis of the oral cavity, preparations of priority choice would be nystatin ointments or suspensions used orally or administered intravenously (Quindos et al. 2019). Nystatin suspension is the most commonly prescribed remedy for thrush in healthy newborns.

The object of the study: composition of modeled extemporaneous oral suspension from nystatin tablets. The purpose of the study: to model extemporaneous oral liquid drugs from nystatin tablets. The tasks of the study: to develop a scheme for the production of liquid suspensions from tablets; select excipients, evaluate the quality of modeled drugs. The problem of the study: what auxiliary substances - stabilizers and the production scheme will ensure the quality of extemporaneous liquid drugs with nystatin from tablets?

Materials and methods

Nystatin Actavis 500,000 IU tablets were used for the study. Tablets are round, flat, 10 mm in diameter, yellow excipients: microcrystalline cellulose, magnesium stearate, corn starch. For the stabilization of the test suspensions used auxiliary substances hypromellose, gum arabic.

Table 1. Composition of modeled suspensions

Materials, g	Function	Suspensions				
		NS1	NS2	NS3	NS4	NS5
Nystatin, 500 000 IU	Active substance – disperse phase	8 tablets				
Hypromellose	Stabiliser	-	0,50	1,0	0,5	0,5
Gum arabic	Stabiliser, wetting agent	-	-	-	1,0	-
Sodium benzoic acid 0.1%	Preservative	0,1				
Purified water	Disperse medium	to 100.0				

The suspensions were made by dispersing – crushing nystatin tablets to a fine homogeneous powder mixture in a pestle, introducing stabilizer solutions of hypromellose of different concentrations and gum arabic to form a primary pulp, which is then diluted to the resulting disperse system. Nystatin as a substance is hydrophobic, so the stabilizer used and the moisturizer in the suspension must reduce the surface tension. The selected concentrations of hypromellose solutions were 0.5% and 1.0%. Hypromellose forms a viscous dispersed system, and a stabilizing and slowing effect of nystatin sedimentation is expected. Each suspension was produced in 100.0 ml. To determine whether the duration of the crushing time of the tablets affects the quality of the suspensions, suspensions (NS1; NS2; NS3; NS4) tablets were crushed for 1 min. and for NS5 suspension, the tablets were crushed for a total of 3 minutes.

Evaluation of the organoleptic properties of the studied suspensions visually: color, smell, taste, appearance. The test was performed over a period of 2 weeks by keeping the suspensions vertically in tubes of 10 ml under natural conditions at 15°C to 25°C. Assessed after 1 day, 7 days, 14 days after manufacture.

Study of sedimentation rate and volume: suspensions (10 ml) were stored in light, at natural room temperature in graduated tubes vertically. The sedimentation rate is calculated – the volume/time of sediment. The sedimentation volume is calculated as a percentage using the formula: $F = 100\ Vt/Vo$ where: F is the sedimentation volume of the suspension expressed as a percentage (%); Vt is the volume of sediment,

expressed in millilitres (%); Vo is the initial volume of the suspension, expressed in millilitres (%) (Kulshreshtha, 2010).

Resuspendation of suspensions is a quantitative test to assess the lightness of the distribution of suspension sediment in a medium after a long stand (Saad et al. 2016). The time (s) required to convert the deposited system into a suspension was measured by manually turning the container with the suspension at an angle of 180° to the suspension. Measurements were made 2 weeks after manufacture. The suspensions, which required >120 s for resuspendation, were seen as difficult to resuspend, and <120 s for resuspendation were seen as easily resuspending. If the suspension has not been resuspended, it is considered unresuspended.

Research results and discussion

According to the organoleptic properties of the suspensions under study - smell, color, turbidity or transparency, it is possible to evaluate the quality of the formulations. The observation of changes in the organoleptic characteristics of the suspensions under study indicates the stability of the suspensions under study. The results obtained: all the test suspensions after production and observation for 14 days were yellowish in color, had a specific nystatin-weak odor, evenly cloudy, when deposited - the medium is transparent colorless and the sediment turns yellow, and after resuspendation it became a turbid yellowish color. Changes in organoleptic properties due to differences in composition and observation over time are not observed.

In order to produce a high-quality oral extemporaneous suspension, it is necessary to select the appropriate auxiliary substances - stabilizers to avoid or make slowly the sedimentation, creating a viscosity of the medium, and a moistened one that ensures the moistening and distribution of solid nystatin particles in the liquid dispersion medium of the suspension. Properly selected composition and indicators of the suspension must ensure the quality and stability of the manufactured drug. It is important that sedimentation occurs at such a rate that the dosage of the drug is accurate. Sedimentation occurs in a liquid suspension from the very beginning of production, so the influence of excipients must be determined by studying the sedimentation rate of the modeled suspensions. The rate of sedimentation of suspensions decreases with an increase in the viscosity and density of the disperse medium. The stabilizer, which forms a viscous medium in a liquid suspension, was chosen for hypromellose of different concentrations of 0.5% and 1.0%. The study may justify or exclude that the different concentrations of hypromellose in suspensions chosen may form a durable and stable dispersion medium system. The results of the study obtained are presented in Table 2.

Table 2. Results of the sedimentation study

Criterion	Modeled suspensions				
	NS1	NS2	NS3	NS4	NS5
Sedimentation rate, in ml/h within 24 hours after manufacture	0,75	0,22	0,03	0,05	0,25
The volume of sedimentation in ml, after the production of → after 2 weeks.	0,75→0.75	0,5→1,1	0,2→1,3	0,25→0,1	0,5→1,1
Resuspendation time, min, after 2 weeks.	4	2	3	1	3

The results show (Table 2) that the auxiliary substances added to the composition of the suspensions affect the rate and volume of sedimentation and the time of resuspendation. Suspension NS1 does not contain excipients, so the influence of the stabilizer and the humidifier on the stability of the modeled suspensions was determined by comparison. When assessing the sedimentation rate, hypromellose stabilizes the deposition of nystatin particles of the suspension compared to NS1. The concentration of hypromellose in suspensions significantly slowed down the sedimentation rate in direct proportion. The slowest sedimentation occurred in the NS3 and NS4, in which, respectively, hypromellose 1%; 0.5% and gum arabic 1%. When comparing NS2 and NS4, which contain an equal amount of hypromellose, but also contain a gum arabic, the results prove that the moisturizer has an effect on the stabilization of suspensions, i.e. slows down sedimentation. When comparing NS2 and NS5, which have an identical composition, but there was a difference in technology in terms of the duration of crushing nystatin tablets, the difference in sedimentation rates is insignificant, sedimentation occurred at a similar speed. Differences in technology due the duration of crushing nystatin tablets in NS2 and NS5 suspensions did not affect the stability.

The results of the sedimentation volume study (Table 2) showed that the uniform sedimentation volume was obtained in NS1 and NS4, only due to the stabilizer and humidifier, the sediment sedimented more slowly. Interpreting the results of the volume of deposits of NS2, NS3 and NS5 in comparison with NS1, it can be said that the amount of sediment only after production and after 2 weeks depends on the state of the stabilizer and its concentration. The higher the concentration, the smaller the volume of sediment at the beginning of the study and after 2 weeks the volume differs only slightly. Differences in technology regarding the duration of crushing nystatin tablets in NS2 and NS5 suspensions did not affect.

Resuspendation - one of the criteria for determining the stability and quality of the suspension. A quality suspension should be easy to resuspend. Table 2 shows the times needed to restore the suspensive dispersion over the entire volume of the suspension. The study of resuspendation was carried out after 2 weeks of storage. The results of the study showed that all the suspensions under study resuspend, but the time is different from the composition. It took at least time to resuspend the suspension NS4, which contained not only a stabilizer, but also a moisturizer. The longest resuspended suspension NS1, which did not contain a stabilizer. The timing of the crushing of nystatin tablets did not matter to the time of resuspendation.

In order to assess the effect of the selected excipients - stabilizers, their suitability for the stability and quality of suspensions, the percentage of sedimentation of suspensions F is given (Fig. 1)

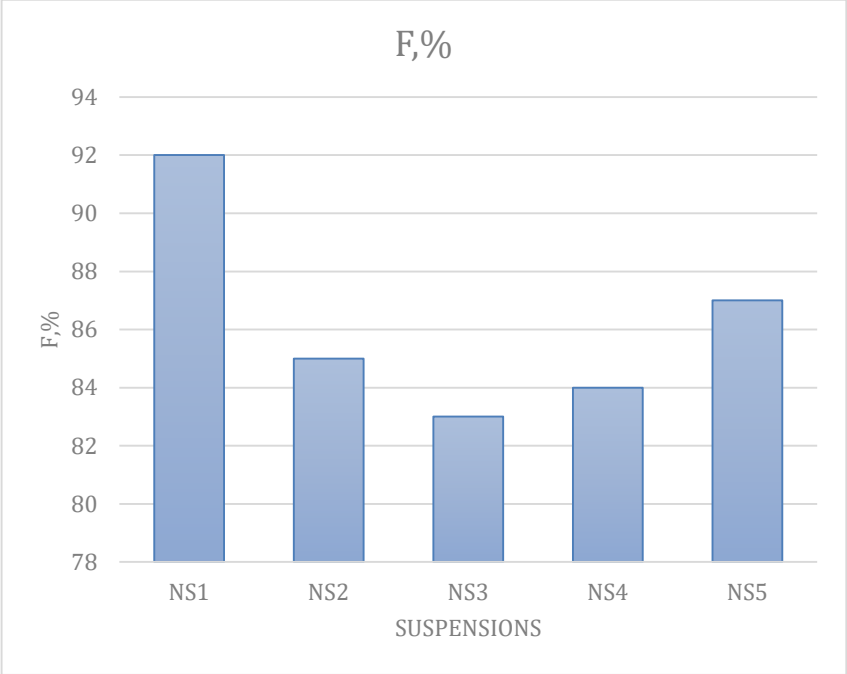

Fig.1. Percentage sedimentation of suspensions, F%

The minimum sedimentation volume indicates that the most stable of all those studied is NS3, for which 1% hypromellose was used to stabilize it. It can be argued that the hypromellose used to stabilize the suspensions under study reduced the formation of nystatin deposits. Suspensions NS3 - disperse medium hypromellose 1% stabilized this suspension in comparison with the NS1 suspension, where the disperse medium is purified water. Accordingly, the disperse medium hypromellose 0.5% solution stabilized NS2 and NS4 and NS5, but to a lesser extent - their sedimentation volume is higher than that of NS3.

Conclusions

Extemporaneous oral suspensions from nystatin tablets were produced by the method of mechanical dispersion, the methodology for the production of suspensions of hydrophobic substances. Suspensions are produced by the mass - volume method. The timing of the crushing of nystatin tablets did not affect the results. Auxiliary substances embedded in the composition of the suspensions - stabilizers hypromellose solution and moisturizer gum arabic stabilized the modeled suspensions: the sedimentation rate slowed down, the volume of sedimentation decreased by volume and percentage (F) within two weeks after manufacture. Study of the modeled suspensions showed that the stabilizer hypromellose and the humectant gum arabic significantly affected the resuspension time. The resuspension time was shortened because the presence of excipients prevented the settling of the suspension particles from forming solid deposits, allowing the patient to easily resuspend the suspension prior to administration, thereby ensuring dose uniformity due to uniform particle distribution throughout the suspension volume.

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