

## COMPOUNDED PREPARATIONS WITH NYSTATIN FOR ORAL AND OROMUCOSAL ADMINISTRATION

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**Abstract:** Therapy of oral, esophageal and gastrointestinal candidiasis is still a common problem that can be solved by an administration of antimycotics. Major disadvantage of registered commercial antifungal medicinal products is their price, so the health care system and its payers may profit from extemporaneous compounding. An appropriate drug therapy for candidiasis (trush) is nystatin, which is a substance available in the Czech Republic for the magistral preparation relatively recently, since 2010. Making formulas for extemporaneous compounding is quite simple and preparations particularly useful for dentists, pediatricians, otolaryngologists, oncologists and gastroenterologists. The authors formulated composition of viscous oromucosal suspension, oral/oromucosal hydrogel and oromucosal gelatine globule which may be present as compounded products containing nystatin for oromucosal and/or oral administration. The preparation is practically verified and magistral products have been already used in clinical practice.

**Keywords:** nystatin hydrogel, nystatin viscous suspension, nystatin oromucosal globule, extemporaneous compounding, compounded (magistral) preparations, candidiasis, pediatric therapy

Since 2010, there has been a significant increase in the amount of medicinal substances with quality certificate usable for extemporaneous preparation (1). New, rational formulas that can substitute for missing manufactured products can be created. Extemporaneous compounding in the Czech Republic increases quantitatively and is of greater importance for the system, similarly to the situation seen in Germany and Switzerland (2, 3). One of the newly available substances is nystatin (*Nystatinum*), produced by VUAB Pharma, a.s., Czech Republic, one of the biggest manufacturers of the substance. This drug is requested by popular demand in topical formulations applied to the skin, as well as in oromucosal and oral dosage forms. In the Czech Republic the range of commercially available formulations is very limited. Ointments containing nystatin for skin application, and vaginal globules containing nystatin in combination with nifuratel, neomycin and polymyxin are the only available products at the moment. In some countries, nystatin

is commonly available in liquid and pastille (lozenge) forms. Thus, extemporaneous compounding represents unique possibility to formulate nystatin preparations in other forms like oromucosal/oral gel, oromucosal globules, oromucosal suspensions, pastes etc.

### Nystatin – properties and uses

Nystatin is a light yellow or brownish powder, hygroscopic, thermolabile, and sensitive to moisture, light, oxygen and extreme pH. It has been prepared by fermentation from *Streptomyces noursei* cultures (2, 4). Nystatin is almost insoluble in water and other common solvents, therefore, it must be suspended in preparations. The pH values of 4.5–6.5 in a milieu have the optimal efficacy. Products containing water should be stored in refrigerator (2–8°C) (2, 4).

Nystatin represents an antifungal antibiotic with fungicidal effect, significantly against yeasts of *Candida*, *Rhodotorula* and *Trichosporon* species;

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sufficiently against *Aspergillus* species. It is not effective against bacteria, viruses and actinomycetes. Nystatin cannot be resorbed by the skin or mucosa and its gastrointestinal resorption is very poor too. Thus, it is preferentially formulated for oral administration. Nystatin has been used as a local antimycotic in mucosal and skin candidiasis. Very important is its treatment action in the mouth cavity (oral candidiasis), pharynx (oropharyngeal candidiasis), esophagus (esophageal candidiasis) and alternatively in distal gastrointestinal tract (intestinal candidiasis). In these cases nystatin is applied oromucosally (locally into mouth) or orally (local effect in the esophagus, bowel). Nystatin is very important in prophylaxis and therapy of mucosal candidiasis in full-term and premature newborns, infants, and in people with high risk of candidiasis (e.g., immunocompromised individuals) (2, 5, 6).

As the drug is produced by fermentation, its relative potency is presented as international units per milligram (IU/mg). However, the relative activity of standard amount of nystatin in various batches is not equal and therefore, the pharmacist has to calculate the appropriate amount of backfill according to the actual potency of individual batch.

Nystatin has a wide variety of applications in dermatology, oropharyngology, gynecology, gastroenterology, pediatrics, oncology and dentistry. Treatment of candidiasis (mostly oromucosal, esophageal and intestinal) is still a difficult task in some patients since the therapy with specific manufactured antimycotics (fluconazole, itraconazole) may lead to a number of possible drug-drug interactions. Furthermore, the treatment cost is also an important issue. For example, extemporaneously compounded preparations with nystatin are more cost effective and thus pharmaco-economically more acceptable for the health care system. Due to the poor absorption of nystatin in gastrointestinal tract there are no drug-drug interactions and systemic adverse effects. The use is safe in children, including newborns and infants, as well as in patients after transplantation or other special populations.

Nystatin is indicated for prophylaxis and treatment of fungal (candidal) focal infection in candidate subjects for transplantation, especially in total denture wearers. Nystatin, not only due to the minimal risk of incidence of drug interactions with immunosuppressive remedies (mainly interaction between triazole antifungals and cyclosporin A) but also for its acceptable costs (7), is the first choice in treatment of oropharyngeal candidiasis after transplantation.

The most commonly used activity in finished preparations is 100 000 IU/g. The recommended

dosage in oromucosal candidiasis is 200 000 – 600 000 IU four times a day in children and adults, and 100 000 – 200 000 IU four times a day in newborns and infants. Dose of 100 000 IU four times a day is considered adequate for premature newborns and newborns with low birth weight (8). The drug should be kept for certain time in the mouth because of sufficient contact with the mucosa. In intestinal candidiasis, the doses are usually 0.5 – 1.5 million IU three times a day, and 150 000 – 300 000 IU three times a day in infants. Nystatin should be administered after a meal and the usual treatment duration is 5 to 10 days. The treatment should continue at least 48 h after the symptoms disappear.

## EXPERIMENTAL

### Compounding formulas of oromucosal/oral preparations containing nystatin

The formulas from German Neues Rezepturformularium (NRF) (2) that includes standardized formulas containing nystatin oromucosal isotonic water suspension without preservatives, nystatin oromucosal glycerol suspension and dermal preparations based on hydrophilic cream and zinc oxide oil suspension, were an inspiration for authors. The new formulas were created: nystatin oromucosal viscous suspension with preservatives, nystatin oromucosal/oral hydrogel, and nystatin oromucosal gelatin globule. Dosage syringe is used for suspension dosage, oromucosal gel is dosed by a graduated measure, pressing out from polypropylene cup with piston or from a tube. Globules represent divided pharmaceutical dosage form. Oromucosal suspension and hydrogel contain 100 000 IU nystatin per gram.

### Formula No. 1: Nystatin oromucosal viscous suspension with preservatives

Nystatinum (6660 IU/mg)	0.6
Hypromellosem (app. v. 17350)	0.24
Glycerolum 85%	1.2
Menthae piper. etherol.	gutt. IV
Aq. conservans	ad 40.0

This formula is adapted from standardized NRF formula. The suspension is approximately isotonic as the one from NRF, but it contains antimicrobial additives (Aqueous solutions of parabens, conservation water, Aqua conservans) and hydroxyethylcellulose (hyetelose) is replaced by another viscosity increasing substance – hypromellose. Its apparent viscosity (app. v.) should be included in the name of the preparation, since there are hypromelloses of various viscosities on the market. Nystatin

content is related to the relative potency that should be presented in brackets. Pharmacist shall calculate the nystatin content in the event of different efficacy of the batch used. Taste of the preparation is adjusted by mint essential oil. The essential oil is not necessary, but without it the preparation is slightly bitter. The shelf life of the suspension without preservatives is 14 days according to NRF (2). The shelf life of suspension with preservatives is expected to be at least 1 month. Nystatin, in suspension, is relatively stable when stored in a refrigerator. This suspension is unsuitable for newborns and infants due to the content of parabens and the mint essential oil. A preparation without parabens and mint essential oil is to be used for newborns and infants. The product is intended for oromucosal use while gel is more suitable for oral use (see formula No. 2). However, the swallowing of suspension is possible.

#### Preparation technique

In a beaker, hypromellose is flooded by 15 g of hot conservation water and is suspended under permanent mixing. The mixture is kept to cool under occasional gentle mixing, until hypromellose swells up and a weakly turbid slime is created. The evaporated water is replenished and mint oil is added. Nystatin is smeared with glycerol, in parts cooled hypromellose slime is added to the mixture, remaining conservation water is replenished and the whole suspension is well mixed.

#### Formula No. 2: Nystatin oromucosal/oral gel

Nystatinum (6 660 IU/mg)	1.5
Hypromellosum (app. v. 17 350 mPa.s)	1.8
Xylitolum	10.0
Glycerolum 85%	5.0
Aq. conservans	ad 100.0

This is an improved preparation published previously (1). It contains parabens as preservatives, which prolong the shelf life, and gel forming substance hypromellose that shows higher bio-adhesive effects than e.g., methylcellulose. Xylitol is preferable as anti-caries substance, moreover it adjusts the taste of the preparation. The preparation is used primarily in oncology patients suffering from candidiasis after radiotherapy of head and neck. These patients are at an increased risk of caries supported by xerostomia. Solid pharmaceutical dosage forms (e. g., lozenges) should be avoided not only due to the risk of mechanic injury to the mucous membrane, but also due to uneasy dissolution in mouth when the function of salivary glands is inhibited by radiotherapy. Further, the preparation may be used for the treatment of intestinal candidiasis. In this

case, the preparation should be kept in the mouth for some time and swallowed a bit later, since the Candidas are present in esophagus and mouth cavity too. Total of 5 g of hydrogel contains 0.5 g of xylitol and 500 000 IU of nystatin.

#### Preparation technique

In a beaker, hypromellose and xylitol are flooded by 70 g of hot conservation water. Xylitol is dissolved and hypromellose is suspended under permanent mixing. The mixture is gently mixed until gel forming, after cooling evaporated water is added. Nystatin is smeared with glycerol, in parts cooled hypromellose gel is added to the mixture, remaining conservation water is replenished and the whole gel is well mixed.

#### Formula No. 3: Nystatin oromucosal gelatine globules

Nystatinum (6 660 IU/mg)	2.25
Gelatin	21.0
Glycerolum 85%	48.0
Xylitolum	9.0

Aq. conservans q. s.

ut fiant globuli oromucosal. No. XXX (triginta).

#### Preparation technique

Gelatine, glycerol, xylitol and conservation water are used for matter hot preparation. Nystatin is suspended in molten matter and globules are poured out, each gelatine globule contains 500 000 IU of nystatin. The globule dissolves only slowly and thus the contact time of the drug with the mucous membrane is prolonged.

The stability of nystatin preparations are still under research. Stability of nystatin is depended on pH, temperature, light and heavy metal ions. Previous studies (2, 9) showed that nystatin suspensions are stable for 3 months when stored at 2–8°C and light protected. At the room temperature (25–28 °C) or 37°C the stability of suspension was much lower.

#### CONCLUSION

Since nystatin is available as a substance, it is possible to prepare required pharmaceutical dosage forms in local pharmacies, primarily for oromucosal and oral use in candidiasis. Extemporaneously compounded drugs containing nystatin are effective, and in comparison to the commercial medicinal products containing specific antifungals also cheaper and without a risk of drug interactions. Off-label use of vaginal tablets, sometimes realized in clinical prac-

tice in the case of oral candidiasis, can be avoided with the use of oromucosal nystatin preparations. Oncology patients also benefit from the softness of the preparations for weakened oral mucosa. Presented preparations should be stored in a refrigerator at 2–8°C. Upon refrigeration, no discoloration of nystatin, showing its decomposition, is observed for a period of 1 month. Longer shelf life could be guaranteed after examination of physical-chemical stability, possibly microbial stability. The presented formulas could form, after verification of their stability, a basis of standardized formulas.

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