



# Stability Study of Extemporaneously Compounded Nitrofurantoin Oral Suspensions for Pediatric Patients

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Received: 29 July 2021 ♦ Accepted: 20 Sep 2021 ♦ Published: 31 Oct 2022

**Citation:** Pehlivanov I, Stoeva S, Simitchiev A, Stefanov S, Andonova V. Stability study of extemporaneously compounded nitrofurantoin oral suspensions for pediatric patients. *Folia Med (Plovdiv)* 2022;64(5):807-816. doi: 10.3897/folmed.64.e72334.

## Abstract

**Aim:** To evaluate the stability of nitrofurantoin suspended in different extemporaneously compounded vehicles after storage at 4°C and at 25°C. To formulate an effective, readily available vehicle that can guarantee extended stability and precise dosing.

**Materials and methods:** Nitrofurantoin was suspended at a concentration of 10 mg/mL in seven different vehicles compounded of different blends of Syrupus simplex, sorbitol 70%, methylcellulose 1%, gummi arabici 1%, gummi xanthani 1%, and sodium carboxymethylcellulose (NaCMC) 1%. Samples of 100 mL of every compounded suspension were stored in dark in graded glass bottles at 4°C and at 25°C. Samples were analyzed at the beginning and every 10 days up to day 30 and every 30 days after. Variations of physical properties such as sedimentation, ease of resuspension, color and odor were evaluated visually and organoleptically. Rheological analysis was also performed in order to determine suspensions' behavior during storage and dosing. Variations in nitrofurantoin concentration and pH were evaluated with suitable analytical procedure (UV-Vis; HPLC; pH/ORP). Microbiological stability was evaluated via incubation on suitable culture media.

**Results:** To the 30th day, only three of the compounded suspensions exhibited significant physical stability and slight change in taste and odor stored at both temperatures. Two samples stored at 25°C exhibited nitrofurantoin concentration greater than 95% and 4 samples stored at 4°C – concentration greater than 95%. All models showed no microbial growth up to day 30. At 120 days, only three of the compounded suspensions, stored at 4°C, exhibited relatively high nitrofurantoin concentrations: 88.2%, 92%, and 81.1%, respectively. Only one model suspension showed chemical and physical stability ( $\geq 95\%$  of the initial concentration) for 102 days. No model suspension remained sterile after 30 days.

**Conclusions:** The suspensions compounded with vehicles of blends of syrups, xanthan, croscarmellose (NaCMC), and sorbitol exhibited low to none sedimentation, good uniformity of content and are suitable organoleptically for pediatric administration. The model suspension stored at 4°C (NTF VII 4°C – with major excipients: sucrose 16%, sorbitol 17%, xanthan gum 0.25%, NaCMC 0.25%) stands out with nitrofurantoin concentration higher than 95% along with no or little signs of sedimentation. After adding a suitable preservative agent or system, a formulation with these characteristics might have an expiration date of at least 90 days.

## Keywords

microbiological stability, NaCMC, rheological analysis, xanthan gum

## INTRODUCTION

The bacterial infections caused by antibiotic-resistant microorganisms are a health issue gaining substantial importance in recent years. These kinds of conditions are challenging to treat, which leads to increased morbidity and mortality. Nitrofurantoin (NTF) has been successfully used in urinary tract infections in adult (>65 years), pediatric, and pregnant patients in the past 50 years. Recently, due to the growing problem of antibiotic resistance, there has been an increase in the interest in this drug as a potential treatment for various infections caused by antibiotic-resistant pathogens.<sup>[1]</sup> This is a confirmation of the tendency to use already known drugs with new applications because of the changed distribution and resistance of some pathogens.<sup>[2]</sup> Nitrofurantoin is included in the 20th edition of the WHO model list of essential medicines in the group of antibacterial agents.<sup>[3]</sup> Nitrofurantoin is frequently prescribed to children (<14 years) and adults (>65 years), usually as oral suspension.<sup>[4]</sup>

According to data from local pharmacies and pediatricians in the city of Varna and hinterland (unpublished) between 2018 and 2021, 42 pediatric patients needed extemporaneously compounded NTF.

At present, in Bulgaria, there are no registered medicinal products containing NTF as an active pharmaceutical ingredient (API). This situation forces patients to travel to other countries to provide the needed medicine, encouraging illegal smuggling and unauthorized distribution through internet sites. Few authorized pharmacies in Bulgaria can compound oral suspension with NTF. These pharmacies use more often crushed tablets or capsules as sources of NTF supplied by one of the ways mentioned above rather than the raw substance largely because of the supply difficulties. The formulation of the compounded substance by a magisterial prescription is rarely indicated on the label, more often due to proprietary claims and commercial secrets. On the other hand, there is a risk of adverse reactions to any of the excipients if a given patient is sensible and unaware of its presence in the formulation.

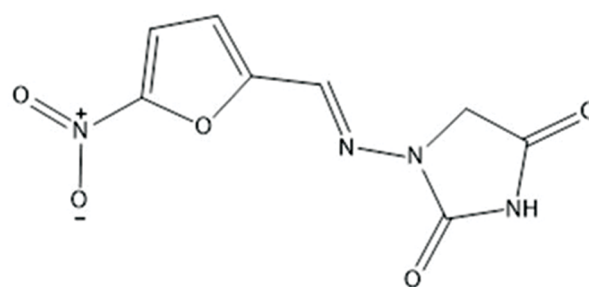
Generally, the stability attributed to extemporaneously compounded liquid forms is often limited to 30 days, the reason for that being that usually there is no exact information on the stability of the different active ingredients in the various liquid vehicles used in the different pharmacies. In Bulgarian pharmacies, Syrupus simplex is primarily used as a vehicle for liquid oral dosage forms since it is economical and easily prepared. Structural and suspending agents, such as NaCMC or Arabic gum, are rarely included in such formulations. When formulated in Syrupus simplex or glucose syrup, NTF oral preparations exhibit poor organoleptic and gastrointestinal discomfort, as reported by many patients. This is due to the high sugar concentration and near to neutral pH of the dosage form.

The unpleasant organoleptic properties of an oral suspension can compromise the patient's adherence to the therapy. That is a big issue with pediatric patients. There

are different taste and odor masking strategies, such as artificial sweeteners, cyclodextrin complexes, crystal coating, etc.

In the present study, we used excipients such as natural sweeteners, viscosity enhancing agents, and a combination thereof with the scope to mask the typical bitter taste of NTF. When used in appropriate concentrations, different sugars and viscosity-enhancing excipients can successfully increase the vehicle viscosity. Hence, the contact between the drug and the taste buds is limited due to limited diffusion through the saliva. Regarding bitterness, the use of sweeteners, some amino acids, or flavor enhancers on their own does not give satisfying results, as shown by some studies.<sup>[5-8]</sup>

NTF is a chemotherapeutic agent belonging to nitrofurans introduced to clinical practice in 1952. NTF is a synthetic antimicrobial agent active on both Gram-positive and Gram-negative microorganisms, obtained by the addition of a nitro group and hydantoin to a furan, a synthetic derivative of imidazolidinedione (**Fig. 1**). NTF is a weak acid ( $pK_a=7.2$ ), and its solubility is pH-dependent and appears as odorless lemon-yellow crystals or fine yellow powder with a bitter taste. It is very slightly soluble in water and ethanol, and it is soluble in DMF (1:16) and acetone (1:200). NTF darkens on contact with alkalis and sunlight exposure. It decomposes in contact with all metals, except aluminum and stainless steel. NTF must be stored in airtight closed containers away from sunlight and at room temperature ( $t<25^\circ\text{C}$ ). NTF oral suspensions are stable at pH 4.5–6.5 and must not be frozen. The usual dosage regimen is 50 mg or 100 mg, four times a day for 7–10 days. For pediatric patients, the dosage may vary between 3–7 mg/kg/day. Some of the most common adverse effects, which are carried by the GI tract, are anorexia, nausea, and vomiting. These effects usually manifest themselves in the first week of the therapy.<sup>[9,10]</sup>



**Figure 1.** Nitrofurantoin structure.

## AIM

The present study aims to formulate a vehicle for an oral liquid dosage form that is easy to prepare and use, economical, and mainly to assure optimal shelf-life stability of NTF extemporaneously compounded in an oral suspension.

## MATERIALS AND METHODS

### Chemicals and reagents

Nitrofurantoin (99.5%, AlfaAeser), sorbitol (93%, Orion-Mateevi ltd), xanthan (99%, Orion-Mateevi ltd), NaCMC (99%, Orion-Mateevi ltd) were generously donated by Pharmakon Pharmacy, Varna. Sucrose, Arabic gum, methylcellulose, Na<sub>2</sub>HPO<sub>4</sub>, and citric acid (Ac.CITR) (99%, Valerus) were also used in the studied formulations.

### Composition and preparation of nitrofurantoin model vehicles

NTF was suspended at a concentration of 10 mg/mL in seven different liquid vehicles using porcelain mortar, which is previously cleaned and sterilized. The suspensions were prepared aseptically. Preservatives of any kind were not included in the formulations. NTF was suspended in different vehicles and combinations of them, such as Sir. simplex (65%), Sir. sorbitoli (70%), mucillago methylcellulosae (1%), mucillago gummi arabici (1%), mucillago gummi xanthani (1%), mucillago NaCMC (1%).<sup>[11-17]</sup> The full list of excipients and the combinations of them are summarized in **Table 1**.

Aliquots of 100 mL of every formulation were put in airtight closed graduated flasks stored at dark and 4°C and 25°C. At selected times, samples were taken in triplets and stored at -18°C to establish the NTF stability in the different vehicles.

### UV-Vis spectrophotometric determination of nitrofurantoin

The preliminary quantification of NTF in the suspension models was performed spectrophotometrically using BOECO S-26 spectrophotometer ( $\lambda=367$  nm) with a 10-mm quartz cuvette. Nitrofurantoin obeys the Lambert-Beer law in the concentration range 20-40  $\mu\text{g/mL}$  and at wavelengths of 330 nm to 400 nm. Acetone was used as solvent.<sup>[9,18-20]</sup>

To prepare the stock solution, 1.000 g NTF was dissolved in acetone in a 100.0-mL graduated flask (S1).

In order to determine the wavelength of maximum absorption ( $\lambda_{\text{max}}$ ), 1 mL of the stock solution was transferred in 100.0 mL graduated flask and bidistilled water was added up to 100.0 mL. The resulting solution (10  $\mu\text{g/mL}$ ) was scanned through wavelengths from 330 nm to 400 nm. For construction of the calibration curve, we prepared six solutions with respective concentrations: S2=0.005 mg/mL, S3=0.01 mg/mL, S4=0.015 mg/mL, S5=0.02 mg/mL, S6=0.025 mg/mL, and S7=0.03 mg/mL. The absorbance at every point was measured in triplets.

### Sedimentation volume monitoring

The samples were stored in a 100.0-mL graduated flask. The sedimentation volume of the models stored at 4°C and 25°C, respectively, was determined visually. The extent of sedimentation was determined as cake volume to initial suspension volume ratio ( $H=\text{cake volume/suspension volume}$ ). The supernatant transparency also was evaluated visually. The number of 180° inversions to reach the resuspension of the cake also was determined.

### pH determination of nitrofurantoin suspension models

The pH values of the models were determined with pH/ORP Meter (HANNA Instruments HI2215) without dilution.

### Rheological analysis

The rheological behavior of the products was investigated using a rotating viscometer Brookfield RV-DV II + Pro (Brookfield AMETEK, USA) with an accuracy class of 1% equipped with a small sample adapter, including a metal scraper cylinder with an SC4-13R water jacket and a cylindrical spindle with a conical head SC4-27. The cylinder was filled with a sample of 10.4 mL. All experiments were performed at a fluid temperature of 20°C $\pm$ 0.1°C. For this purpose, a Zeamil Horyzont thermostat with a temperature

**Table 1.** Excipients used to formulate the vehicles containing nitrofurantoin 10 mg/mL

Excipients	Sample sign							
	NTF I	NTF II	NTF III	NTF IV	NTF V	NTF VI	NTF VII	
SIR. SIMPLEX 65%	100%	-	25%	25%	25%	25%	25%	
SIR. SORBITOLI 70%	-	100%	25%	25%	25%	25%	25%	
MUCILLAGO METHYLCELLULOSE 1%	-	-	50%	-	-	-	-	
MUCILLAGO GUMMI ARABICI 1%	-	-	-	50%	-	-	-	
MUCILLAGO GUMMI XANTHANI 1%	-	-	-	-	50%	-	25%	
MUCILLAGO NaCMC 1%	-	-	-	-	-	50%	25%	
Ac.CITR/Na <sub>2</sub> HPO <sub>4</sub> BUFFER (q.s.)	+	+	+	+	+	+	+	
GLYCEROL (q.s.)	-	-	-	-	+	-	+	

range of 0 to 100°C±0.1°C was used. The temperature of the sample was monitored by a temperature probe with a range of 0°C to 100°C±0.1°C connected to the viscometer. Once the range of shear rates was established, the software product Rheocalc 32 generated a viscometer work program. In this study, an experiment was generated at twenty shear rates from 3.4 s<sup>-1</sup> to 68 s<sup>-1</sup>. Each shear rate was held for one minute, after which the program reported a value for apparent viscosity and shear stress. All experiments were performed in triplets.

To describe the flow behavior of the models, the experimental data (shear rate – shear stress) were fitted by Power law (Eq. 1) and Herschel-Bulkley (Eq. 2) models:

$$\tau = k.D^n \quad (1)$$

where  $\tau$  is the shear stress (Pa),  $k$  is the consistency index (Pa.s<sup>n</sup>),  $D$  is the shear rate (s<sup>-1</sup>), and  $n$  is the flow behavior index (dimensionless).

$$\tau = \tau_0 + k.D^n \quad (2)$$

where  $\tau$  is the shear stress (Pa),  $\tau_0$  is the Herschel-Bulkley yield stress (Pa),  $k$  is the consistency index (Pa.s<sup>n</sup>),  $D$  is the shear rate (s<sup>-1</sup>), and  $n$  is the flow behavior index (dimensionless).

### Determination of variation in nitrofurantoin concentrations in the model suspensions through reverse-phase high-efficiency liquid chromatography (RP-HPLC/UV)

#### Instruments

The analysis was performed with a high-performance liquid chromatographic – Thermo Scientific UltiMate 3000 Analytical LC System, equipped with a quaternary pump (Thermo Scientific Dionex UltiMate 3000 LPG-3400 SD Quaternary Pump), an automatic injector (Thermo Scientific Dionex UltiMate 3000 Autosampler), a variable wavelength vibration detector (Thermo Scientific Dionex UltiMate 3000 VWD), and a diode array detector (Thermo Scientific Dionex UltiMate 3000 DAD-3000 Diode Array Detectors). Data collection and analysis were performed using Chromeleon™ 7.2 chromatographic data software (Thermo Scientific).

#### Chromatographic conditions

Separation of compounds was achieved using a Thermo Scientific HYPERSIL GOLD AQ C18 (150×4.6 mm, 5 μm) analytical column, protected by an HYPERSIL GOLD AQ C18 (10×4.6 mm, 5 μm) guard-column. The method used isocratic elution with a mobile phase consisted of 65% potassium dihydrogen phosphate buffer (10.0 mmol/L): 35% acetonitrile (v/v), the flow rate was 1.0 mL/min. The temperature of the columns and the autosampler were

maintained at 30°C and 25°C, respectively. The total duration of each run time was 10 minutes. The volume of sample injection was 20 μL.

The qualitative and quantitative determination of NTF was made according to the substance's retention time and UV spectrum in standard samples. Quantitative analysis was performed using the method of external standardization.

#### Sample preparation

All samples were stored at –18°C until analysis. Different quantitative determinations were performed at time intervals of t=0, 10, 20, and 30 days and then every 30 days until a concentration less than 95% (nominal one) was established.

The samples were subjected to ultrasonic extraction three times (with 2.0 mL of acetone each time), and the fractions were filtered with a 0.45 μm Minisart® Sartorius filter. 100 μL of the NTF acetone concentrates were evaporated to dryness under a gentle stream of N<sub>2</sub>, using a concentrator SBH CONC/1 equipped with a block heater SBH130D/3 (Cole-Palmer Ltd., UK). The dry residues were reconstituted in 5.0 mL of freshly prepared distilled water. The samples were homogenized on a vortex mixer (ZX3 Advanced, Italy) and centrifuged (Ohaus Frontier FC5706, USA) at 5000 rpm for 5 minutes. 50 μL of the aqueous solutions were transferred to vials (2.0 mL, ND 8 mm, Thermo Scientific™, USA) and diluted to 1.0 mL with freshly prepared double distilled water (Gesellschaft für labortechnik mbH, Germany).

#### Validation of the HPLC method

The validation of the HPLC method was performed following the criteria of the ICH Topic Q2 (R1) guideline (ICH Topic Q2 (R1)).<sup>[21]</sup>

#### Microbiological stability

The microbiological stability of the models was also tested. For this purpose, the models were prepared aseptically and stored in sterile flasks. No antimicrobial preservatives were included in the formulations because of an antimicrobial agent, NTF, and the high theoretical osmolarity of the vehicles (~800 mOsmol/L). Every day, the flasks were left open for 60 seconds to mimic the prescribed dose withdrawal process. Microbiological samples were taken every 7 days and cultured until positive. The culture media used are Blood agar, MacConkey agar, Chocolate agar, Saburo agar, CHROM® agar. FUNGIFAST® (ELITech Group, Italy) was also employed to determine the presence of fungi, molds, and yeasts.

#### Statistical analysis

The measurements of absorption ( $\lambda = 367$  nm) of the solutions with known concentration were performed in triplets. The calibration curve was built using the mean values of the measurements. The calculated standard deviation of the measurements was  $1 \times 10^{-3}$  to  $2 \times 10^{-3}$ . The standard equation

was obtained with the least squares method. The coefficient of determination ( $R^2$ ) was calculated.

## RESULTS

The following variables were monitored:

- Changes in concentration and pH;
- The extent of sedimentation;
- Apparent viscosity (visually);
- Ease on resuspension (number of inversions);
- Color and odor (organoleptically);
- Rheological analysis;
- Microbiological contamination.

### Preliminary UV-Vis spectrophotometrical determination of content uniformity of nitrofurantoin

The maximum absorption of the NTF standard solution was determined at  $\lambda=367$  nm. The found value is corresponding to those published in different official sources.<sup>[9-18]</sup> At this wavelength, the standard equation is:

$$y = 0.0142x + 0.0003, R^2 = 0.9996 \quad (3)$$

Where linearity is observed in NTF concentrations range 0.005 mg/mL – 0.025 mg/mL (Fig. 2).

This UV-Vis spectrophotometric procedure was used to determine the content uniformity of NTF in the different model suspensions. The determination was performed 30 days after preparation of the models, both on those stored at 4°C and 25°C. The obtained results are summarized in Table 2. Results indicate that NTF concentration did not change significantly in the models containing viscosity modifiers in their formulation and stored at 4°C.

### Sedimentation volume monitoring

The results from the monitoring of variations of the sedimentation volume are reassumed in Fig. 3. As can be seen from the graph, the models NTF V, VI, and VII present the

slowest sedimentation. They need the least number of inversions to resuspend independently of temperature (Fig. 4).

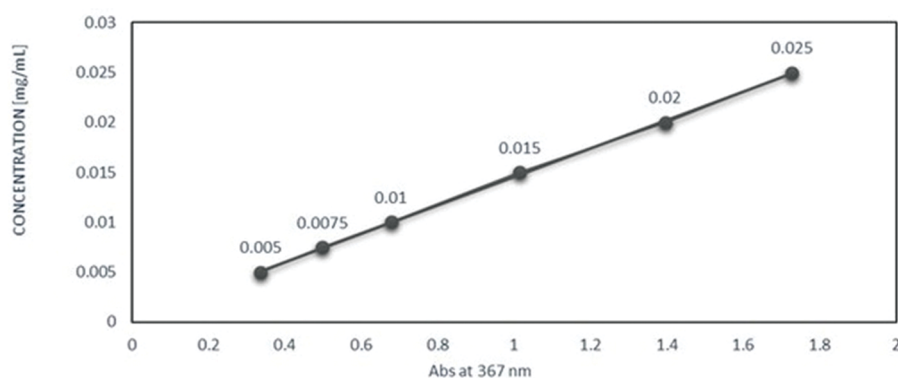
### Rheological analysis

The shear rate vs. shear stress rheogram for samples tempered at 4°C and 25°C are shown in Figs 5A, 5B. A non-newtonian shear thinning behavior was observed for all cases. The highest values of shear stress were observed in sample NTF VII.

The flow index under the Power law is a measure of deviation from the Newtonian behavior of the products. If the product is Newtonian  $n=1$ , if it is pseudoplastic  $n<1$ , and dilatant  $n>1$ . As the value of  $n$  is close to 1, the product has more Newtonian behavior (i.e., viscosity does not depend on the shear rate). The flow behavior indices for Power-law ( $n<1$ ) confirm the shear-thinning behavior of the samples. This also indicates that the samples have pseudoplastic

**Table 2.** Content uniformity of NTF in the different model suspensions after 30 days

MODEL	Storage temperature	Concentration (mg/mL)
NTF I	25°C	5.6
NTF II	25°C	9.4
NTF III	25°C	7.5
NTF IV	25°C	1.7
NTF V	25°C	9.388
NTF VI	25°C	9.431
NTF VII	25°C	10.52
NTF I	4°C	7.13
NTF II	4°C	8.88
NTF III	4°C	10.4
NTF IV	4°C	9.620
NTF V	4°C	9.643
NTF VI	4°C	9.672
NTF VII	4°C	11.10



**Figure 2.** Calibration curve of nitrofurantoin.



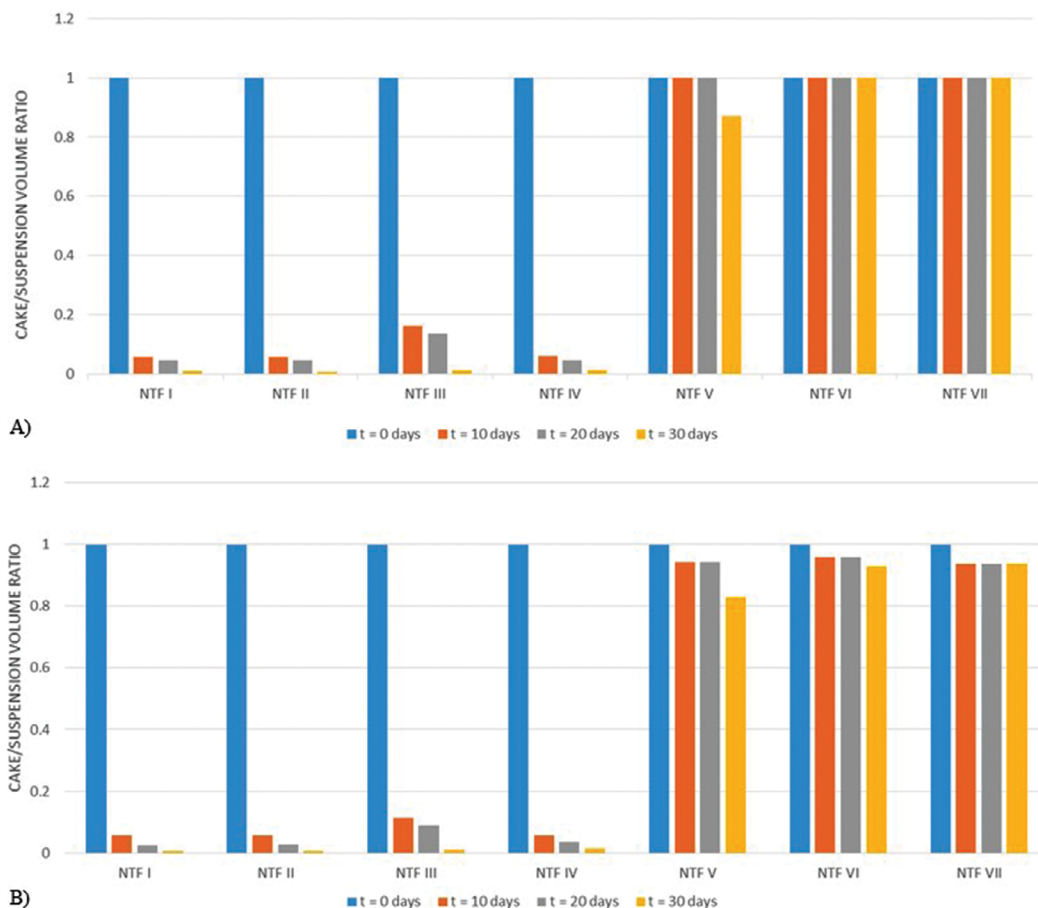


Figure 3. The extent of sedimentation of the models stored: A) at 4°C and B) at 25°C.

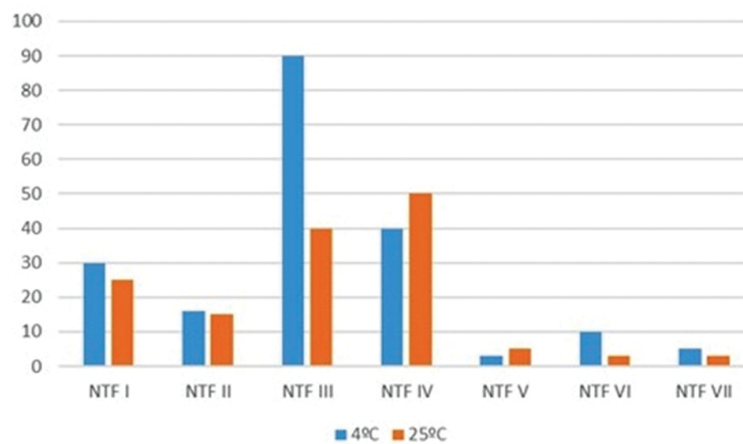


Figure 4. Number of 180°-inversions to resuspend.

character and distinguish with an inversely proportional relation between effective viscosity and shear rate.

Consistency index is an indicator of the effective viscosity of the products at shear rate  $D = 1 \text{ s}^{-1}$ . The experimental results revealed that sample NTF VII.4°C had the highest viscosity.

The Herschel-Bulkley model was used to determine the yield stress  $\tau$ , Pa. It provides information about the amount of stress that the fluid may experience before it begins to flow. The experimental results show that samples NTF VI.4°C and NTF VI.25°C had the lowest obtained values. This observation alarms about the low physical stability of these two suspensions.

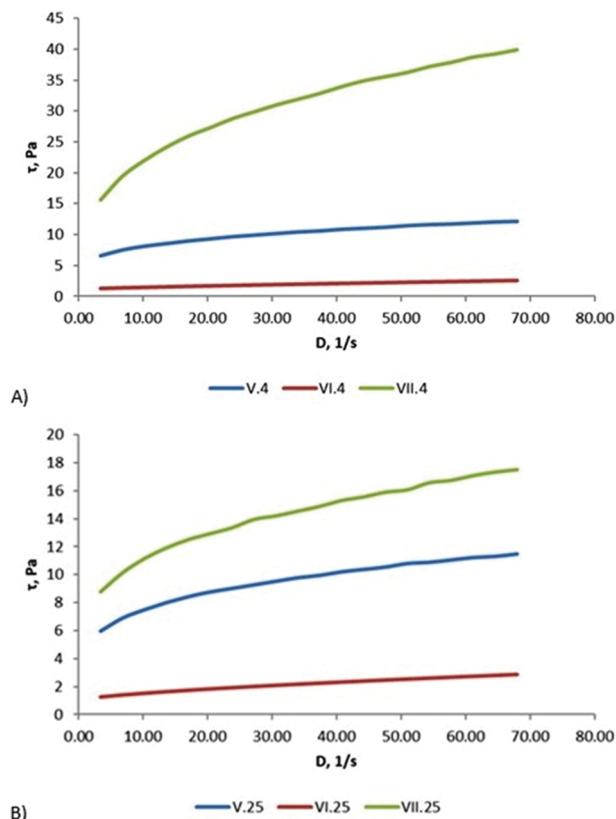


Figure 5. Rheogram for samples stored: A) at 4°C and B) at 25°C

### Determination of variation in nitrofurantoin concentrations in the model suspensions through reverse-phase high-performance liquid chromatography (RP-HPLC/UV)

The reliability of the analytical results was confirmed by the established acceptable values of trueness ( $b \leq 0.010\%$ ) and precision ( $RSD \leq 0.28\%$ ). The linearity was estimated by the straight-line equation ( $y = ax + b$ ) and the correlation coefficient ( $R^2$ ). To construct the calibration curve, a series of freshly prepared standard samples with a concentration of 0.1, 0.5, 1.0, 1.5, and 2.0  $\mu\text{g}/\text{mL}$  were analyzed three times. As a result, the value of  $R^2$  was equal to 0.9996. The quantification (LOQ) limit of NTF was found to be 0.05  $\mu\text{g}/\text{mL}$ , referring to a signal-to-noise ratio ( $S/N \geq 10$ ).

In addition, there was performed a comparison of series of blank and standard samples. The conducted specificity tests confirmed the ability of the system to detect the target analyte in the presence of concomitant components derived from the sample (Fig. 6).

After data collection, two graphs (Figs 7A, 7B) were constructed. The graphs indicate the NTF stability suspended in the three model vehicles after the physical stability evaluation (sedimentation and rheological behavior). The stability criterion limit was set at 95% or above of the initial NTF concentration according to CHMP, which is a

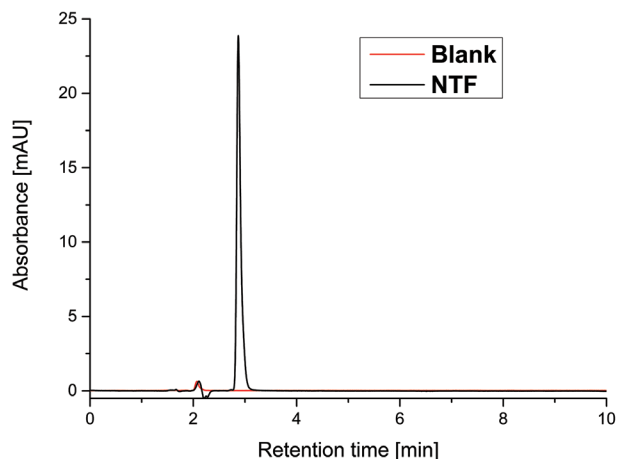


Figure 6. Nitrofurantoin chromatogram.

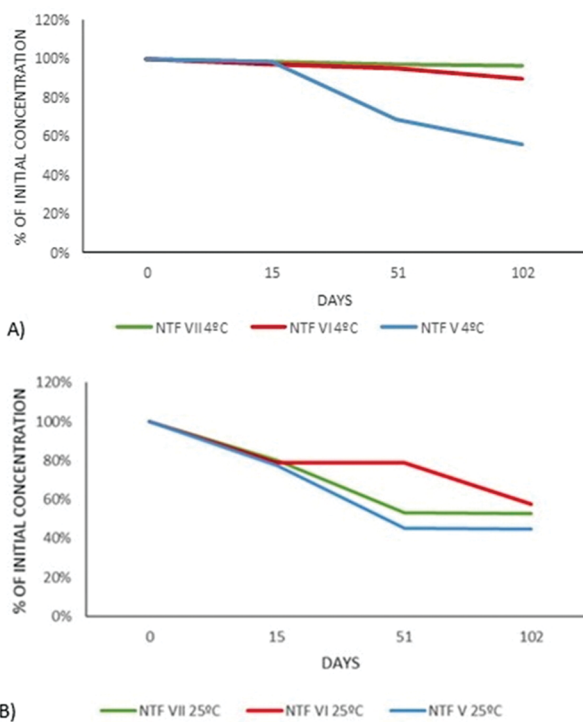


Figure 7. Change in NTF concentration in the model suspensions A) at 4°C and B) at 25°C.

stricter criterion than those used by other authors in similar researches.<sup>[22,23]</sup>

### Microbiological stability

All model suspensions remained sterile until the 30<sup>th</sup> day after compounding. No other microorganisms were detected except *Candida Glabrata*, a fungus to which the vehicles represent an optimal ambient to develop (pH~5 and high simple carbohydrates content). The identified fungus presents microbial count in the different models as shown in Table 3:

**Table 3.** Microbial count of *C. glabrata* colonies

	NTF V	NTF VI	NTF VII
Stored at 25°C	2.3×10 <sup>6</sup>	1.9×10 <sup>6</sup>	2.0×10 <sup>6</sup>
Stored at 4°C	2.0×10 <sup>6</sup>	2.9×10 <sup>6</sup>	2.1×10 <sup>6</sup>

## DISCUSSION

In this study, we found that the majority of model suspensions stored at 4°C (fridge) as well as the models NTF V, VI, and VII stored at 25°C (room temperature) are chemically stable ( $\geq 95\%$ ) up to 30 days after preparation. Following the chromatographic analysis, only one model suspension (NTF VII 4°C) stands out with NTF concentration higher than 95% one hundred and two days after compounding. The low kinetic constant of hydrolysis justifies this trend at low temperatures.<sup>[24]</sup>

The rheological analysis and the sedimentation volume determination show that the NTF VII 4°C model presents the highest viscosity, which is an important prerequisite to physical stability and assured dosing uniformity. The model vehicles with high viscosity would assure limited contact of NTF with the taste buds, which would improve the organoleptic properties and the bitter taste masking. Furthermore, the inclusion of viscosity-enhancing excipients in the formulations such as xanthan gum and NaCMC could predispose a sustained release of the drug to a degree; hence, complete absorption and less GI irritation could be expected.<sup>[25-29]</sup>

## CONCLUSIONS

The inclusion of viscosity-enhancing excipients and others in the formulation of the oral suspension with NTF can significantly improve the compounded preparations' physical and chemical stability. Abandoning the simplistic approach to use Syrupus simplex as a vehicle and considering the use of excipient such as xanthan gum or NaCMC is a valuable path to improve the stability of the compounded product and patient compliance. These excipients are inexpensive and would not raise the price of the final product.

Further research should be done to enhance the microbiological stability over 100 days, similarly to the chemical stability of the NTF suspension achievable without the use of aggressive and toxic preservatives.

## Acknowledgements

The authors have no support to report.

## Funding

The authors have no funding to report.

## Competing Interests

The authors have declared that no competing interests exist.

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# Исследование стабильности пероральных экстенпоральных суспензий нитрофурантоина для пациентов педиатрического профиля

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**Дата получения:** 29 июля 2021 ♦ **Дата приемки:** 20 сентября 2021 ♦ **Дата публикации:** 31 октября 2022

**Образец цитирования:** Pehlivanov I, Stoeva S, Simitchiev A, Stefanov S, Andonova V. Stability study of extemporaneously compounded nitrofurantoin oral suspensions for pediatric patients. Folia Med (Plovdiv) 2022;64(5):807-816. doi: 10.3897/folmed.64.e72334.

## Резюме

**Цель:** Оценить стабильность нитрофурантоина, суспендированного в различных экстенпоральных суспензиях после хранения при 4°C и 25°C. Разработать эффективную, легкодоступную суспензию, гарантирующую длительную стабильность и точное дозирование.

**Материалы и методы:** Нитрофурантоин суспендировали в концентрации 10 mg/mL в семи различных суспензиях, состоящих из различных смесей Syrupus simplex, 70% сорбита, 1% метилцеллюлозы, 1% гуммиарабика, 1% ксантановой камеди и 1 % карбоксиметилцеллюлозы натрия (NaCMC). Пробы по 100 mL каждой приготовленной суспензии хранили в темноте в градуированных стеклянных склянках при 4°C и 25°C. Образцы анализировали в начале и каждые 10 дней до 30-го дня и каждые 30 дней после. Изменения физических свойств, таких как седиментация, лёгкость ресуспендирования, цвет и запах, оценивали визуально и органолептически. Также был проведён реологический анализ для определения поведения суспензий при хранении и дозировании. Изменения концентрации нитрофурантоина и pH оценивали с помощью подходящей аналитической процедуры (UV-Vis; HPLC; pH/ORP). Микробиологическую стабильность оценивали путём инкубации на подходящих питательных средах.

**Результаты:** К 30-му дню только три из приготовленных суспензий демонстрировали значительную физическую стабильность и незначительное изменение вкуса и запаха при хранении при обеих температурах. В двух образцах, хранившихся при 25°C, концентрация нитрофурантоина превышала 95%, а в 4 образцах, хранившихся при 4°C, концентрация нитрофурантоина превышала 95%. Все модели не показали микробного роста до 30-го дня. Через 120 дней только в трёх составных суспензиях, хранившихся при 4°C, наблюдались относительно высокие концентрации нитрофурантоина: 88.2%, 92% и 81.1% соответственно. Только одна модельная суспензия показала химическую и физическую стабильность ( $\geq 95\%$  исходной концентрации) в течение 102 дней. Ни одна модельная суспензия не оставалась стерильной через 30 дней.

**Заключение:** Суспензии, смешанные с носителями из смесей сиропов, ксантана, кроскармеллозы (NaCMC) и сорбита, показали низкую седиментацию или её полное отсутствие, хорошую однородность состава и органолептически подходят для применения в педиатрии. Модельная суспензия, хранившаяся при 4°C (NTF VII 4°C – с основными вспомогательными веществами: сахароза 16%, сорбит 17%, ксантановая камедь 0.25%, NaCMC 0.25%), выделяется концентрацией нитрофурантоина более 95% при отсутствии или проявления в незначительной степени признаков седиментации. После добавления подходящего консерванта или системы состав с такими характеристиками может иметь срок годности не менее 90 дней.

## Ключевые слова

микробиологическая стабильность, NaCMC, реологический анализ, ксантановая камедь