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# Pharmacist
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Medication issues are the top cause of complaints in aged care. How can pharmacists turn the tide?

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FIVE-YEAR VISION FOR PHARMACY

# NITROFURANTOIN SUSPENSION

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Nitrofurantoin is a nitrofuran antibacterial[1] that acts by inhibiting bacterial protein, DNA, RNA and cell wall synthesis.[2] It is used in the treatment of uncomplicated lower urinary tract infections (UTIs), including prophylaxis or long-term suppressive therapy in recurrent infections.[1,2] Nitrofurantoin is also indicated, although not as first-line treatment, for uncomplicated UTIs in children.[3]

In Australia, nitrofurantoin is available as 50 mg and 100 mg capsules.[4] A nitrofurantoin oral liquid is not marketed in Australia but may be available through the Special Access Scheme (SAS).[2,3] For patients with difficulties swallowing capsules, a compounded oral liquid may be an appropriate alternative to mixing medicine with food or drink, which can make it difficult to assess how much of a dose has been taken,[3] or provide convenient dosing for paediatric populations.[3]

## Active pharmaceutical ingredient (API)

Nitrofurantoin ($C_8H_6N_4O_5$, molecular weight (MW) = 238.2 g/mol) (**Figure 1**), appears as lemon-yellow, odourless crystals or fine powder, that is very slightly soluble in water and in alcohol.[1] Solubility definitions are shown in **Table 1**.

It exhibits pseudopolymorphism and may exist as two monohydrates (hydrates I and II). Pseudopolymorphism refers to different crystal types that are the result of hydration. In the case of nitrofurantoin, hydrate II is more stable, due to its slightly lower solubility.[5] »

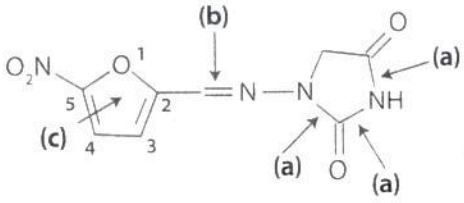
### LEARNING OBJECTIVES

AFTER READING THIS ARTICLE, PHARMACISTS SHOULD BE ABLE TO:

- Recognise precautions that need to be taken by the pharmacist and considerations to take into account when preparing nitrofurantoin suspension
- Explain how to prepare nitrofurantoin suspension extemporaneously, including the components, methods of preparation, packaging, storage and labelling
- Counsel patients/carers on the appropriate use of nitrofurantoin oral suspension and precautions to be taken.

Competencies (2016) addressed: 1.1.3, 1.1.5, 1.3.1, 1.5.1, 1.5.3, 1.5.4, 1.6.1, 3.1.2, 3.2.3, 3.2.5, 3.4.1, 3.4.2, 3.4.3, 3.4.4, 3.4.8, 4.4.5, 4.5.2, 4.5.3
Competencies (2010) addressed: 1.1.1, 1.2.1, 1.2.2, 1.4.1, 3.3.2, 3.4.1, 3.4.2, 4.2.1, 4.2.2, 4.2.3, 4.3.1, 4.3.3, 5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.1.5, 5.1.6, 5.2.1, 7.1.4.
Accreditation number: CAP1809C

**FIGURE 1. Chemical structure of nitrofurantoin**




Sites for alkaline hydrolysis (a), and photolytic degradation (b); and the 5-nitrofuran moiety (c)

Nitrofurantoin is a weak acid (pKa 7.2), which is poorly soluble at the normal pH of the gastrointestinal (GI) tract. Thus, dissolution rate, absorption and bioavailability are dependent on particle size.[6] However, rather than reducing particle size to improve bioavailability, in the 1960s tablets containing microcrystalline drug particles were largely replaced by capsules containing macrocrystalline particles of nitrofurantoin (*Macrodantin*).

This is due to the GI side effects which appear to be related to the 5-nitrofuran moiety (see structure labelled (c) in **Figure 1**) within the nitrofurantoin molecule. Studies demonstrated the switch to the macrocrystalline form, theoretically producing lower drug concentrations in the blood, led to roughly 50% reduction in GI side effects and improved tolerance.[7]

Nitrofurantoin is susceptible to alkaline hydrolysis (by cleavage of the amide bond) at the sites shown in **Figure 1**, although during forced degradation studies by Ferreira et al dilution in both acid (0.1M HCl at 25 °C) and base (0.1M NaOH at 25 °C) resulted in 73.56% and 100% degradation, respectively.[8]

This concurs with the findings from Ertan et al[9] who reported for the first time, as early as 1993, that the drug was unstable in both simulated gastric and intestinal media.[9] Nitrofurantoin is also susceptible to light and the primary degradation process for all nitrofurans, including nitrofurantoin, involves photo-induced hydrolysis at (b), shown in **Figure 1**.[10] Decomposition also occurs on contact with metals.[1]

## Formula, method and stability of oral liquid preparations

The *Australian Pharmaceutical Formulary and Handbook 24th edition* (APF24)[11] provides a formula for a 10 mg/mL nitrofurantoin suspension. This was shown to be stable by Ensom et al[12] for 91 days when stored in amber plastic prescription bottles at 4 °C (refrigerated) and 25 °C (room temperature).[12] In the Ensom et al[12] study, nitrofurantoin suspension was prepared by crushing commercially available nitrofurantoin 50 mg tablets and resuspending the powder in a 1:1 mixture of *Ora-Sweet* and *Ora-Plus*.

A recent study by Ferreira et al8 evaluated the stability of a 2 mg/mL nitrofurantoin suspension in *SyrSpend SF PH4*, a vehicle manufactured by Fagron. Pure API was used and the liquid was stored in low-actinic, light resistant prescription bottles at controlled refrigerated (2–8 °C) and room temperature (20–25 °C).

The suspension was shown to be stable (API above 98%) at both storage conditions for 90 days. The formula and method of preparation for nitrofurantoin oral suspension (2 mg/mL), shown in **Figure 2**, is adapted from Ferreira et al.[8]

Pure drug powder is the preferred source of API, although adult solid dose forms (e.g. emptying capsule contents) can be used provided they are suitable and the stability of the product is considered.[11]

The excipients in solid dosage forms (e.g. *Macrodantin* capsules include maize starch, purified talc and lactose[4]) should also be considered for the potential effect on the bioavailability and stability of the liquid preparation.[11]

The highest available strength of capsules should be used wherever possible to minimise the amount of capsule excipients.[11] It is also important to avoid grinding capsule contents when preparing the oral suspension in order to maintain the macrocrystalline form of nitrofurantoin.

## Excipients

Commercially available vehicles are a convenient resource for pharmacists. The formulas for the original range of commercial vehicles, namely *Ora-Sweet*, *Ora-Plus* and *Ora-Sweet SF*, are available in the United States Pharmacopoeia/ National Formulary (USP-NF) as *Vehicle for Oral Solution NF*, *Vehicle for Oral Suspension NF*, and *Vehicle for Oral Solution, Sugar Free NF* respectively. The ingredients for these vehicles are also referred to in APF24.[6] New proprietary vehicles are now available, such as those supplied by Fagron including *SyrSpend SF PH4*, *SyrSpend SF* and *SyrSpend SF Alka*.[13]

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**TABLE 1. Solubility definitions**

| DESCRIPTION | VOLUME (mL) OF SOLVENT NEEDED TO DISSOLVE 1 g OF SOLUTE |
|---|---|
| **Very soluble** | less than 1 part |
| **Freely soluble** | from 1 to 10 parts |
| **Soluble** | from 10 to 30 parts |
| **Sparingly soluble** | from 30 to 100 parts |
| **Slightly soluble** | from 100 to 1,000 parts |
| **Very slightly soluble** | from 1,000 to 10,000 parts |
| **Practically insoluble** | more than 10,000 parts |

**Example:** 1 g of a very soluble substance will dissolve in less than 1 mL of solvent

**FIGURE 2. Nitrofurantoin 2 mg/mL oral suspension formula and method of preparation**

| NITROFURANTOIN (2 MG/ML) ORAL SUSPENSION (100 ML) | |
|---|---|
| **Nitrofurantoin** | 200 mg |
| ***SyrSpend SF PH4*** | to 100 mL |

**Method**

- Weigh the API into a mortar of sufficient size.
- Add a small amount of the vehicle to wet the powder and mix to a uniform paste. To maintain the macrocrystalline particle size, DO NOT grind capsule powder.
- Continue adding most of the vehicle using the method of doubling (geometric dilution) and mix thoroughly to form a smooth mixture.
- Transfer to a tared, child-resistant, amber prescription bottle.
- Rinse the mortar with the remaining vehicle and make up to the final volume.
- Shake well and label.

Adapted from Ferreira et al[7]

*SyrSpend SF PH4* is a newer commercially available product that is free of sugars, alcohol, parabens, sorbitol, gluten and colourants.[14] It is formulated with modified food starch, preserved with <0.1% sodium benzoate, buffered to pH 4.2, has an osmolality <50 mOsmol/kg[14] and is available unflavoured or in cherry flavour. The *SyrSpend SF* range also includes a preservative-free powder for reconstitution and an alkaline suspending vehicle (*SyrSpend SF Alka*) for acid-unstable APIs.[13] »

# CLINICAL SOLUTIONS THROUGH COMPOUNDING

**FIGURE 3.** Cautionary advisory labels for nitrofurantoin compounded preparation


Reference: Sansom[11]

## Packaging, storage and labelling

Labelling of compounded products must comply with the relevant state or territory legislation, and should include the approved pharmacopoeial or APF name (where applicable), the name and quantity/concentration of all APIs and any preservatives used, the expiry date, storage details, directions for use and cautionary advisory labels.[11] For nitrofurantoin oral suspension preparation labels J,12, 23, B and D ('until all taken') can be used (see **Figure 3**).[11]

The formula should be protected from light[1] and stored in amber prescription bottles with child-resistant caps. Contact your local supplier for packaging options. Pharmacists should also consider providing dosing aids with oral liquid preparations. Oral syringes may be more suitable for infants and young children, whereas measuring cups are appropriate for older children.[3] The preparation should be stored out of reach of children and pets.

## Role of the pharmacist

In the preparation of compounded products, the pharmacist is guided by the *Professional Practice Standards* and pertinent guidelines,[11] together with the prescriber and the needs of the carer and patient. Compounded products must be prepared and dispensed in a manner that complies with legislative standards and ensures their quality, safety and efficacy.[11]

### FURTHER RESOURCES

More information on compounding is available in the *AP* articles below:

**psa.org.au/australian-pharmacist/ap-november-2017/compounding-topical-promethazine-for-nausea**

**psa.org.au/australian-pharmacist/ap-may-2017/oral-acitretin-suspension**

For all cautionary and advisory label requirements, refer to the *Australian Pharmaceutical Formulary and Handbook 24th edition* (APF24).

The APF24 provides a brief overview of extemporaneous product preparation, including references for important standards and guidelines.[11] Pharmacists must use professional judgment to assess the potential risks to staff and the patient associated with preparing and dispensing a compounded product.

The *Professional Practice Standards* has a *Compounding decision support and risk assessment tool* for assessing risk that is available online (Appendix 7 in the *Professional Practice Standards*).[15]

Pharmacists should use a systematic approach for quality assurance of compounding activities, using principles of good compounding practice. Processes and procedures should be reviewed regularly to identify areas for improvement and the resulting actions should be documented.[11]

## Counselling for patients

It is important to counsel patients and carers on correct use, storage and appropriate disposal of a compounded product.[11] Patient counselling and education may be adapted from Consumer Medicines Information (CMIs) available for commercial products.[4] Patient advice and counselling for nitrofurantoin oral suspension should include:

- providing information about adverse effects, special precautions and important drug interactions for nitrofurantoin, which are outlined in the *Australian Medicines Handbook*[2] and APF24[11] (same as the capsules)
- referring to a doctor immediately if patient has difficulty breathing, develops a cough (acute or chronic pulmonary toxicity) or gets any numbness or tingling (peripheral polyneuropathy) while taking nitrofurantoin[2]
- taking the oral suspension with food or milk to assist in reducing nausea and improving absorption[2]
- avoiding use of antacids or urinary alkalinisers as use at the same time as nitrofurantoin can reduce the effectiveness (antibacterial activity is lost if urine pH is >8)[11]
- advising that nitrofurantoin may discolour urine to a brownish colour,[2] and may also discolour soft contact lenses.[11] Disposable lenses can be worn[11]
- advising that doses should be spaced evenly throughout waking hours (unless on a prophylactic night-time dose).[11] »

**Directions for use**

- Shake well before each use to ensure an accurate dose.[11]
- Use a measuring device/aid (e.g. spoon, oral syringe, cup or dropper) to accurately measure the required dose. Do not to use kitchen teaspoons to measure medicine as they are inaccurate and increase the risk of under- or overdosing.[3] NPS MedicineWise has a useful online resource for advice on how to use oral syringes (**www.amh.net.au/resources/public/measuring-liquid-medicines.pdf**).[16]
- The suspension should be taken with or soon after food.[11]
- The preparation should be stored protected from light in a cool place, and kept away from children and pets.

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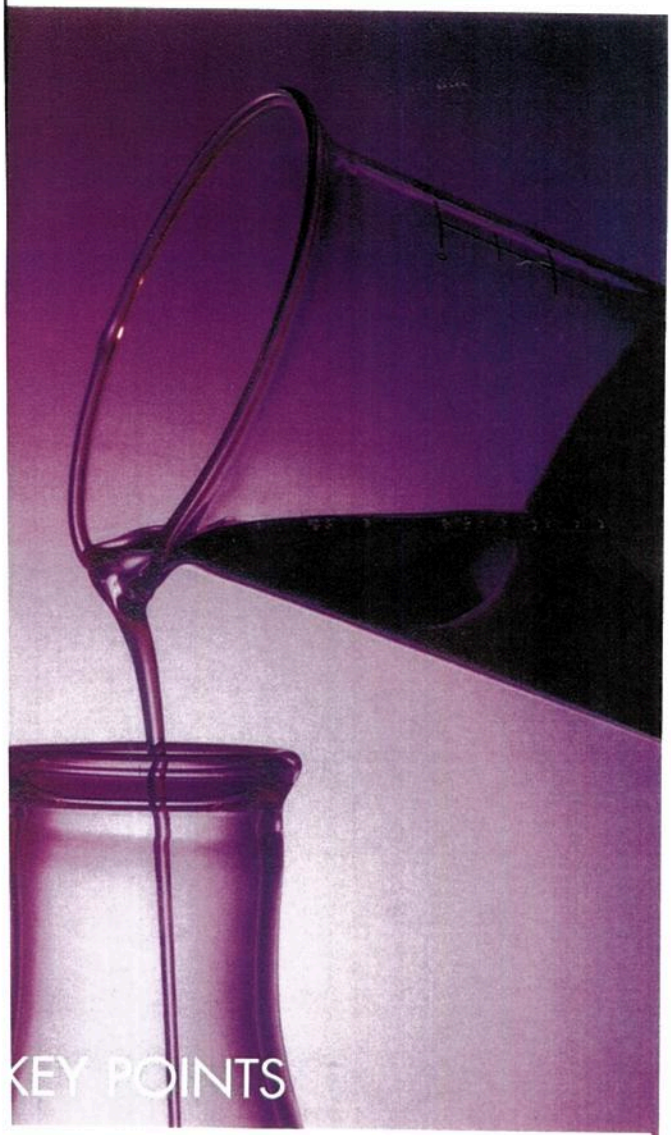

## KEY POINTS

A nitrofurantoin oral liquid is not marketed in Australia, however formulas for nitrofurantoin oral suspension are available. Pure drug powder is the preferred source of API, although adult solid dose forms (e.g. emptying capsule contents) can be used provided they are suitable and the stability of the product is considered. The excipients in solid dosage forms should also be considered for the potential effect on the bioavailability and stability of the liquid preparation.

Nitrofurantoin suspension should be protected from light and stored in a cool place, out of reach of children and pets.

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## Assessment questions

Each question has only one correct answer.

Up to 1 CPD CREDIT Group 2

**1** Solubility of nitrofurantoin monohydrate (form II) in water is 0.11 mg/mL. How many mL of water will be required to dissolve 1 g of the drug?

A) 90.91 mL
B) 909.1 mL
C) 9,091 mL
D) 90,910 mL

**2** Which of the following about *SyrSpend SF PH4* is correct?

A) It contains alcohol.
B) It is buffered to pH 4.2.
C) It has an osmolality >50 mOsmol/kg.
D) It is only available in cherry flavour.

**3** When compounding a product, a pharmacist must consider all the following EXCEPT:

A) That the compounded product complies with legislative standards and ensures quality, safety and efficacy.
B) The potential effect of excipients on the bioavailability and stability of the liquid preparation when using commercially available solid dosage forms to compound.
C) The potential risks to staff and the patient associated with preparing and dispensing a compounded product.
D) That the compounded product be labelled with the name and quantity/concentration of all excipients and any preservatives used, the expiry date and storage details.

**4** A prescription for nitrofurantoin 10 mg/mL oral suspension is received by your pharmacy. Which of the following statements is CORRECT?

A) Take on an empty stomach at least 30 minutes before food.
B) Urinary alkalinisers should be used at the same time as the suspension.
C) Shake the suspension well before use and take the dose with or soon after food using a measuring aid.
D) The suspension may be safely stored within reach of children and pets.