

EVALUATION OF THE STABILITY OF MIXTURES OF PHENHYDAN® CONCENTRATE FOR INFUSION WITH PHENHYDAN® SOLUTION FOR INJECTION

V. Humbert-Delaloye^{1,2}, L. Berger¹, A. Pannatier^{1,2}
¹Pharmacie du CHUV, CH-1011 Lausanne

²School of pharmaceutical sciences, University of Geneva, University of Lausanne, Quai Ernest-Ansermet 30, CH-1211 GENEVA 4

Introduction

Phenhydan® (phenytoin sodium) is often used in the ICUs of our hospitals to treat generalized seizures. Two formulations of Phenhydan® with different uses are available in Switzerland :

- **Phenhydan® concentrate for infusion (CFI), with 750 mg phenytoin/50 ml**, buffered with trometamol (pH=12.5), to be diluted in 500 ml NaCl 0.9% (NS) or Dextrose 5% (D5) before use

and

- **Phenhydan® solution for injection (SFI) with 250 mg phenytoin/5 ml**, no buffer, dilution before use prohibited due to a risk of crystalline precipitation.

The loading infusion dose of phenytoin is 15-20 mg/kg body weight, meaning that one bottle of the CFI is usually not enough while two are too many and excess is lost.

We observed that Phenhydan® was often misused (dilution of SFI, mixing of CFI + SFI). Despite many attempts (e.g. specific information, replacement with another drug), no solution was found to avoid such misuses.

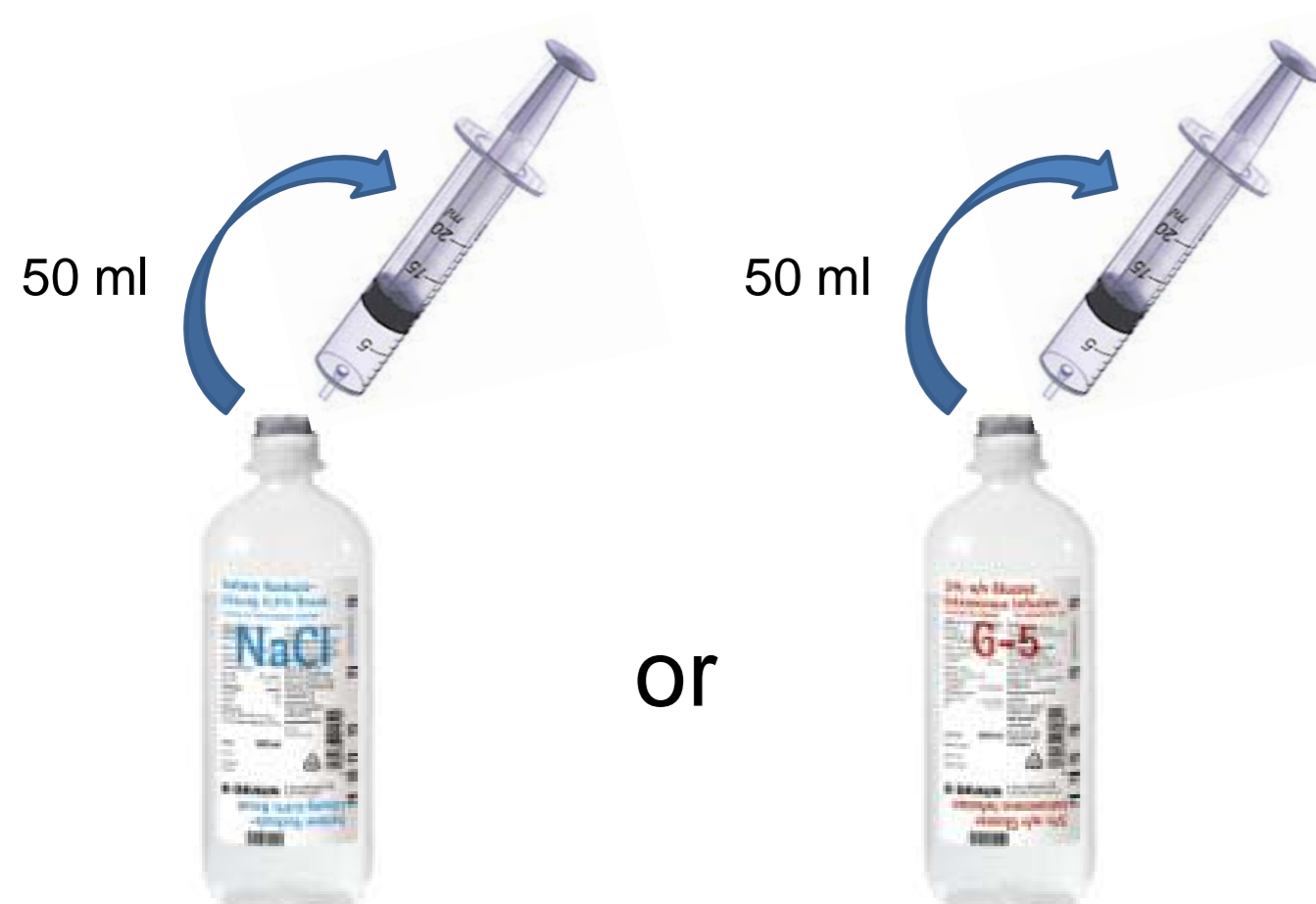
We therefore examined whether the SFI could be mixed with the CFI despite official information advising against diluting the former (Swiss Compendium of Drugs). Should this mixture prove stable, it would allow to complete the content of one CFI (750 mg) with one or more ampoule(s) of SFI (250 mg) to obtain the wanted dose.

The objective of this study was to evaluate the stability of mixtures containing one bottle of CFI with three ampoule(s) of SFI.

Method

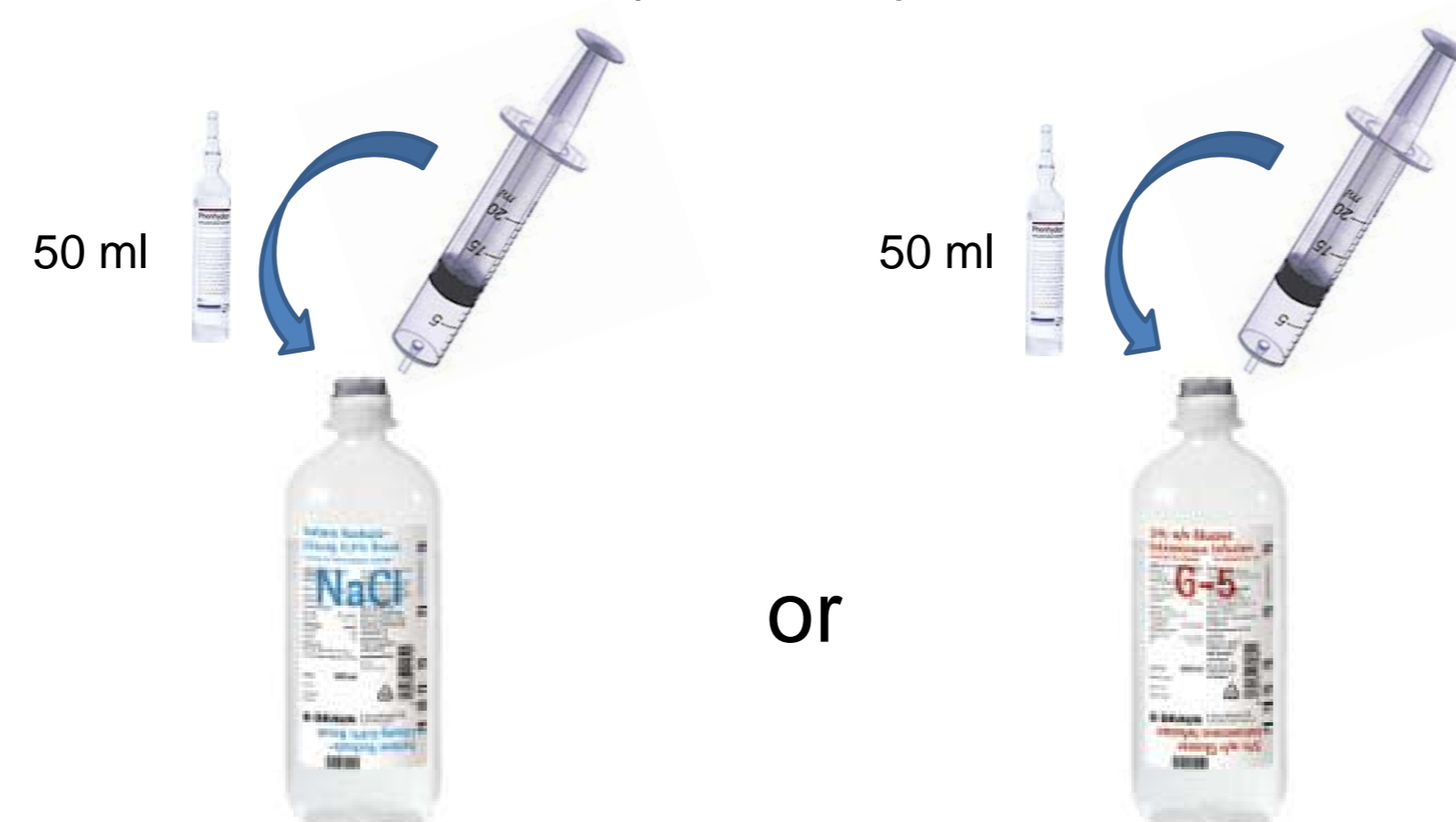
The tests were performed in 500 ml B. Braun Ecoflac® (flac) of NS or D5, as follows :

1. withdrawal of 50 ml of solution from the NS or D5 flac



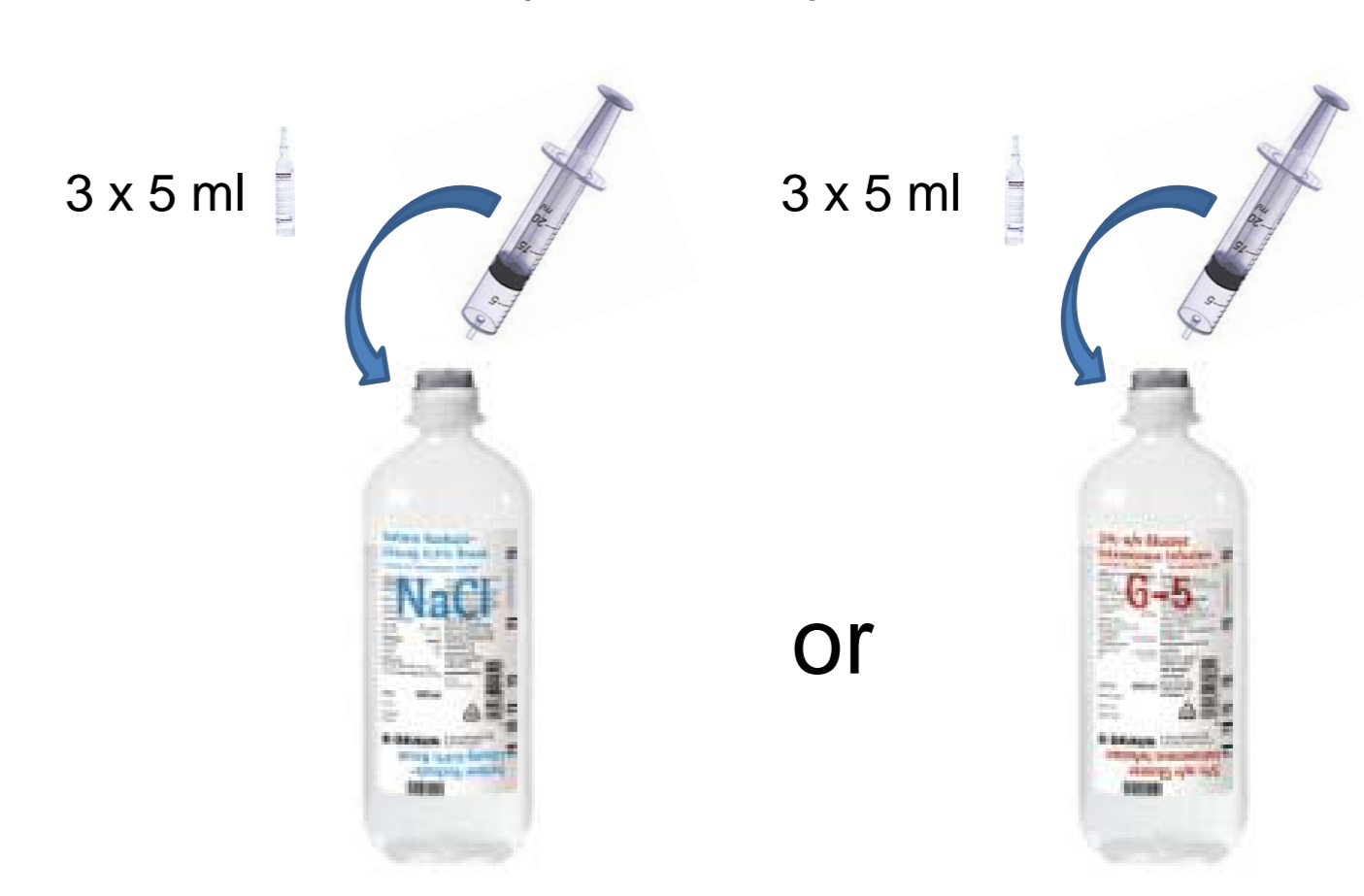
OR

2. addition of one CFI bottle in each flac (= 50 ml)



OR

3. addition of three ampoules of SFI in each flac (= 15 ml)



OR

⇒ the pH was measured after each step and in the final mixture every 24 hours during 120 hours.

⇒ phenytoin concentrations were determined in each mixture after 0, 1, 2, 4, 6, 8, 24 and 120 hours.

Results

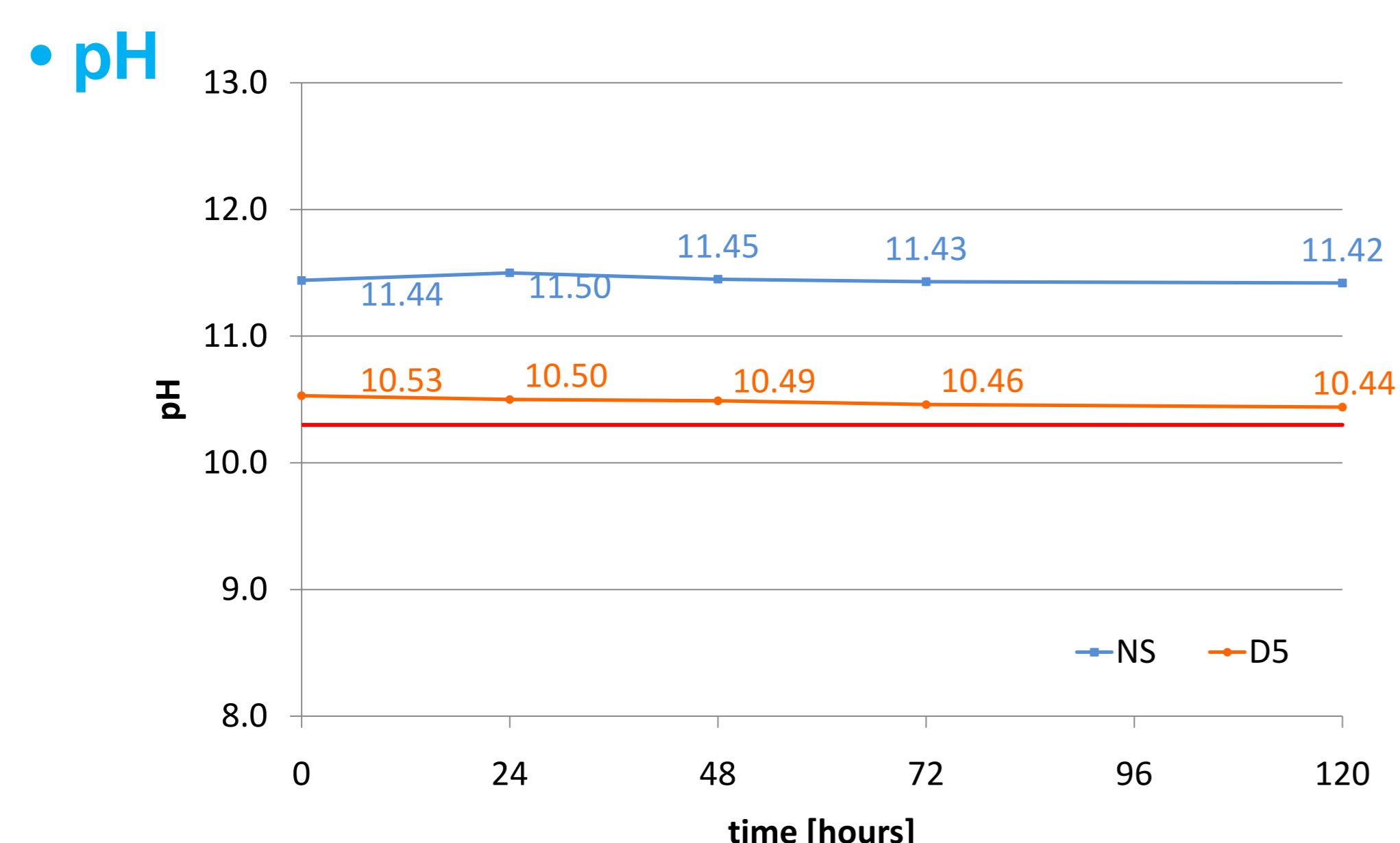


Fig. 1 – evolution of pH over time in the mixtures, the red line being the pH-value under which phenytoin can precipitate

• phenytoin concentration

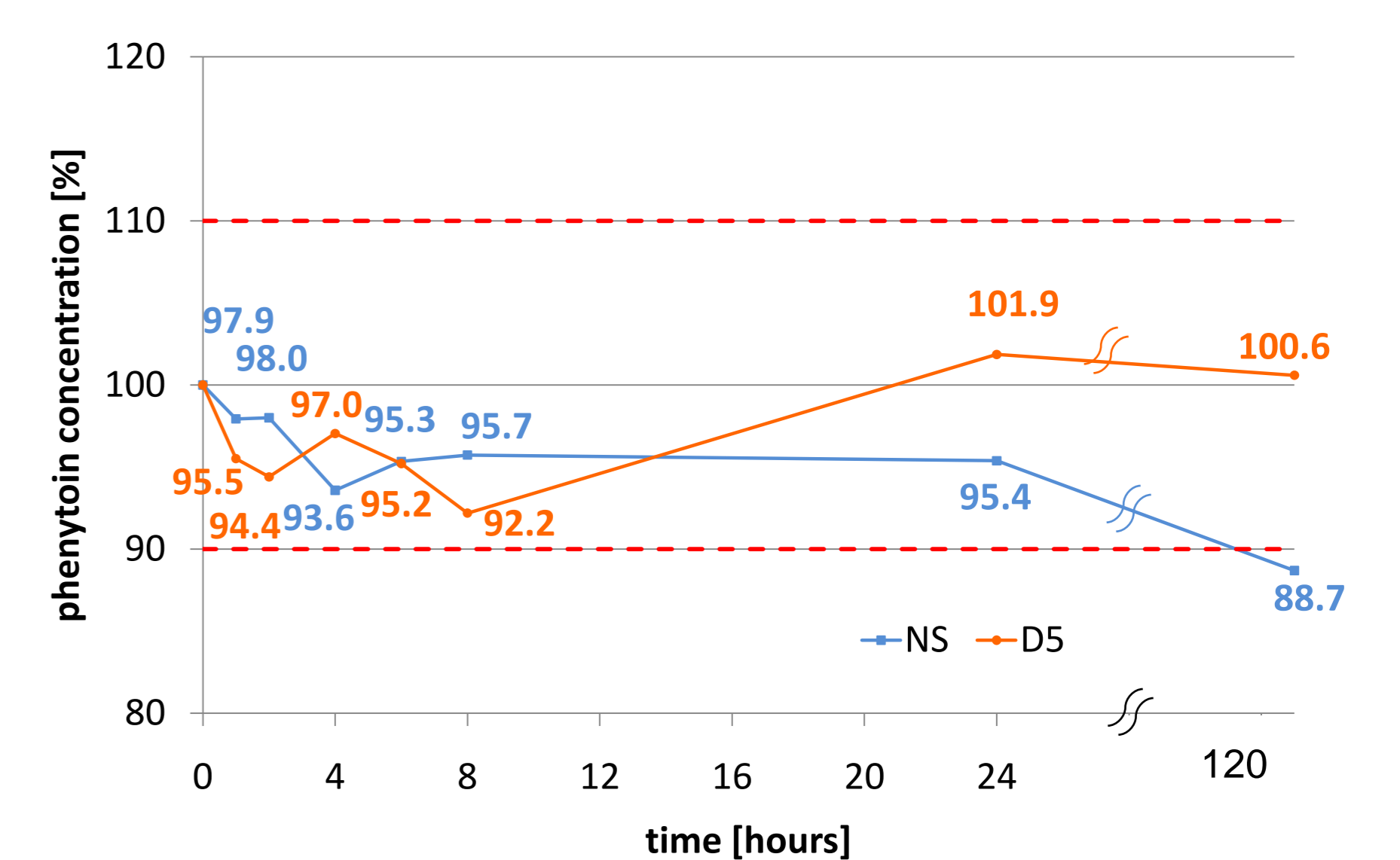


Fig. 2 – evolution of phenytoin concentration over time in the mixtures. The red dotted lines represent the interval of concentrations tolerated by the European Pharmacopoeia

Discussion - conclusion

The pH of the mixtures was stable during at least 120 hours after mixing, for both NS and D5. The pH-value remained over 10.3, thereby avoiding the risk of formation of a crystalline precipitate. Moreover, phenytoin concentrations remained between 90% and 110% (European Pharmacopoeia tolerated values) of the targeted value for over 24 hours without any visible precipitate appearing.

In conclusion, this study proved that this is possible to mix one CFI with up to three SFI in 500 ml of NS or D5 without occurrence of precipitate or significant loss of active substance during 24 hours.