Furosemide ethanol-free oral solutions for paediatric use: formulation, HPLC method and stability study

Lukáš Zahálka,1 Sylva Klovrzová,2,3 Ludmila Matysová,1 Zdenka Šklubalová,2 Petr Solich1

ABSTRACT
Background Oral liquid solutions of the diuretic active ingredient furosemide (FUR) marketed across Europe do not comply with recent requirements for paediatric preparation owing to their ethanol content and, moreover, in some countries only tablet or injection dosage forms of furosemide are available.

Objectives To formulate extemporaneous paediatric ethanol-free solutions of FUR (2 mg/mL) with suitable solubility in the aqueous vehicle and an acceptable taste and to evaluate their stability under two different storage conditions during a 9-month study period.

Methods Our work presents two developed formulations of FUR ethanol-free paediatric oral solutions 2 mg/mL for easy extemporaneous compounding in a pharmacy. FUR solubility avoiding the use of ethanol was achieved using sodium hydroxide (formulation F1) or disodium hydrogen phosphate dodecahydrate (formulation F2). The preparations were stored at 25°C±3°C or at 40°C±0.5°C and protected from light. For FUR and preservative, methylparaben (MP), a stability assay was conducted by a high-performance liquid chromatography validated method and determination of pH stability.

Results The remaining FUR concentration was >90% of the initial concentration after 270 days in both formulations at both storage conditions, 25°C and 40°C. The concentration of MP decreased significantly in the formulation F2 stored at 40°C.

Conclusions Both formulations were stable when stored at room temperature for up to 9 months; formulation F1 was stable even at 40°C. MP used as an antimicrobial agent fully satisfied the recommended criteria for preservative efficacy in oral preparations according to the European Pharmacopoeia 9.0 (5.1.3).

INTRODUCTION
Furosemide (FUR) is a traditional diuretic active agent widely used in adults and in paediatric patients; it is generally administered intravenously or orally. FUR is used in the treatment of hypertension and oedema associated with heart failure, including pulmonary oedema.1 Usually, the oral dose for neonates is 0.5–2 mg per kilogram of weight every 12–24 hours, for children aged from 1 month to 12 years the same dose 2–3 times daily is used, and for children 12 years and above 20–40 mg daily is administered. In resistant oedema, the higher dose can be permitted.1

However, the registered tablets contain at least 40 mg of FUR in one tablet. To achieve the required paediatric dose, it is necessary to crush commercially available tablets, mix the powder with a filler and prepare capsules extemporaneously in a pharmacy. Afterwards, the capsule has to be opened before use and mixed with baby food or liquid before administration. In the Motol hospital pharmacy in Prague, the dose usually prepared for treatment of paediatric patients is 3–5 mg per capsule in agreement with the doctor's prescription.

Liquid preparations are preferred as they have the advantage of more flexible dosing, improved patient and caregiver compliance, and, moreover, are also easier for compounding in a pharmacy.2–4 Registered oral liquid preparations containing FUR cannot generally be recommended for administration in children because of the high-concentration ethanol (EtOH) vehicle used. As examples: Frusol 20 mg/5 mL oral solution (Rosemont Pharmaceuticals Ltd; registered in the UK) contains 10% EtOH, Impugan 10 mg/mL oral drops (Actavis Group hf.; registered in Sweden) contains 9.8% EtOH, and finally LasixR liquid 10 mg/mL (Sanofi-Aventis Deutschland GmbH, Germany) contains 11.9% EtOH.5–7 Using ethanol as the excipient in paediatric drugs does not comply with the general requirements for paediatric preparations1 and is considered unsuitable by paediatric drug committees, drug agencies and published reports.8–13

One, although not optimal, way of preparing FUR oral solutions in a pharmacy is by simply diluting a commercially available registered aqueous injection of FUR with water. The absence of preservatives and the unpleasant taste of the active ingredient are limiting factors for use in oral multidose liquid preparations. If the active pharmaceutical ingredient is available on the market and is freely soluble in water, preparation of an aqueous solution could be considered as the best way for extemporaneous compounding in the pharmacy. However, lower stability of the active pharmaceutical ingredient and excipients could occur in a water solution and a shorter shelf life of the aqueous preparation than with capsules is expected. Therefore, the stability of each drug composition should be determined before administering the preparation to the patients. FUR is a white to slightly yellow, odourless, light-sensitive, crystalline powder with a pK value of 3.9. It is sparingly soluble in ethanol, freely soluble in solutions of alkali hydroxides (pH > 8.0) but, unfortunately, practically insoluble in water or dilute acids.14

The aim of our work was to formulate extemporaneous paediatric ethanol-free solutions of FUR (2 mg/mL) with a suitable solubility of FUR in the aqueous vehicle and an acceptable taste for use in paediatric cardiology and to evaluate their stability.
under two different storage conditions during a 9-month study period. A high-performance liquid chromatography (HPLC) method was developed, validated, and used to determine the concentration of furosemide and the antimicrobial agent methylparaben (MP) throughout the stability period. The main criterion of stability was defined as the retention of at least 90% of the initial concentration of FUR and at least 80% of the initial concentration of MP.

**MATERIALS AND METHODS**

**Materials and chemicals**

FUR, MP, disodium hydrogen phosphate dodecahydrate and sodium hydroxide were obtained from Fagron, Czech Republic; sodium saccharine was obtained from Dr Kulich Pharma, Czech Republic. Water for injection (WFI) was used for the preparation of the extemporaneous oral solutions and their blank solutions; it was obtained from the hospital pharmacy of the University Hospital in Motol, Prague, Czech Republic.

In an analytical study, the following substances were used for preparing the mobile phase and samples: methanol CHROMASOLV gradient grade, acetonitrile CHROMASOLV gradient grade, formic acid 95% and triethylamine 99.5% were obtained from Sigma-Aldrich, Czech Republic; and 18 MΩ.cm ultrapure water from Milli-Q Integral water purification system with an M-pore filter (Millipore, USA).

**Methods**

**Sample preparation**

FUR solutions (2 mg/mL) F1 and F2 were prepared from the furosemide substance and excipients (table 1).

<table>
<thead>
<tr>
<th>Formulations</th>
<th>F1</th>
<th>F2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>0.2 g</td>
<td>0.2 g</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>0.1 g</td>
<td>0.1 g</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>0.024 g</td>
<td>–</td>
</tr>
<tr>
<td>Disodium hydrogen phosphate dodecahydrate</td>
<td>–</td>
<td>1.5 g</td>
</tr>
<tr>
<td>Saccharine sodium</td>
<td>0.1 g</td>
<td>0.1 g</td>
</tr>
<tr>
<td>Water for injection</td>
<td>to 100.0 mL</td>
<td>to 100.0 mL</td>
</tr>
</tbody>
</table>

**Sample preparation**

FUR solutions (2 mg/mL) F1 and F2 were prepared from the furosemide substance and excipients (table 1).

Formulaion 1 (F1) was prepared by dissolving FUR in approximately 2.4 mL of 1% w/v sodium hydroxide solution (60°C, freshly prepared from NaOH and WFI). Sodium saccharine and 50 mL of 0.2% w/v MP solution (prepared by dissolving MP in WFI at 100°C and cooled down) were added and the solution was made up by adding WFI to a final volume of 100.0 mL and transferred to a 100.0 mL amber glass vial with a syringe adapter.

In formulation 2 (F2), FUR was dissolved in approximately 20 mL of disodium hydrogen phosphate dodecahydrate solution freshly prepared from 1.5 g of disodium hydrogen phosphate dodecahydrate and WFI. Sodium saccharine and 50 mL of 0.2% w/v MP solution (prepared by dissolving MP in WFI at 100°C and cooled down) were added and the solution was made up by adding WFI to a final volume of 100.0 mL and transferred to a 100.0 mL amber glass vial with a syringe adapter.

**Instrumentation and analytical assay**

**Liquid chromatography**

An HPLC method was used for the determination of the active pharmaceutical ingredient FUR and the antimicrobial preservative MP in the presence of FUR impurity A (mentioned in the European Pharmacopoeia (Ph. Eur.)) and pharmaceutical excipients used was developed and validated. An integral HPLC system Shimadzu LC-2010C (SW Class VP, ver. 6.13; Shimadzu Corp.) with an octadecyl (C18) silica gel HPLC column (Supelco Discovery HS C18, 150×4.6 mm, 5 μm; Sigma-Aldrich) was used for the chromatographic analysis. The mobile phase consisted of the buffer (1000 mL Milli-Q water, 250 mL formic acid and 750 μL triethylamine; adjusted to a pH of 5.75) and acetonitrile in the ratio 65:35 (v/v); the mobile phase was filtered by a 0.45 μm nylon membrane filter before use. The isocratic flow rate was 1.5 mL/min and the dual absorbance UV detector was set at a wavelength of 270 nm. Chromatograms of standard solution and selected formulation (injection volume 5 μL) are shown in figure 1, and the method validation results are presented in table 2.

**Reference standard solution preparation**

A standard solution was prepared by dissolving the active substance and impurity A in methanol. The final concentrations of the reference standards were 50 μg/mL furosemide and 10 μg/mL impurity A.

**Sample preparation**

An accurately weighed portion of pharmaceutical formulation corresponding to 2.5 mg of FUR (about 1.25 g) was transferred into a 50 mL volumetric flask and methanol was added to 50.00 mL. The solution was mixed and after filtration (0.45 μm-pore filter) was injected into the column and analysed by HPLC.

**Method validation**

The method was validated according to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q2 (R1) guidelines. The system suitability test (ie, repeatability of retention times and areas, number of theoretical plates, resolution, tailing factor), precision, linearity, accuracy, selectivity and robustness were evaluated during method validation (table 2). The parameters of accuracy, precision and selectivity were measured and evaluated for both pharmaceutical formulations.

**System suitability test**

A system suitability test was performed on a standard solution that was injected into the column six times. The reported values are the arithmetic means of six injections.

**Precision**

Six sample solutions were prepared from each of the preparations. Each sample was injected three times. The final results are reported as relative standard deviations (R.S.D) of the FUR and MP peak areas.

**Linearity**

A calibration curve was created using six points that covered the concentration range of FUR from 0.02 mg/mL to 0.8 mg/mL and MP from 0.01 mg/mL to 0.04 mg/mL. Linear regression was used to process the calibration data.

**Accuracy**

The solutions for injection were prepared using a placebo and stock solution of standards instead of the oral preparation. Six solutions were prepared from both preparations. Each solution was injected into the column three times. Accuracy is reported as a parameter recovery with R.S.D.
Selectivity
Selectivity was determined by comparing the chromatograms of the sample solution and standard solution. Figure 1 shows that FUR (ie, the active substance), MP (ie, the antimicrobial agent) and the impurity A are all completely separated from each other and from the saccharine peak in the standard solution and the sample solution. No interference was observed.

Robustness
Various buffer pH values and compositions of the mobile phase were tested. A mobile phase buffer with a pH 5.6 was used with little change in the accuracy (98.50%). The mobile phases from ratio 55:45 (buffer:acetonitrile) are not recommended, because the peaks of FUR and impurity A are not separated. The stability of the standard solution was tested at room temperature without light protection and at 5°C±3°C light protected 24, 48 and 72 hours after its preparation. The accuracy of the peak areas for storage at room temperature without light protection was higher than 1%, and therefore light-protected storage at 5°C±3°C is recommended.

Stability assay and sample analysis
Two batches were prepared for each of the two formulations and each batch solution was divided into four 100 mL amber bottles.

Table 2  Validation results of pharmaceutical formulation F1 and F2

<table>
<thead>
<tr>
<th></th>
<th>F1</th>
<th>F2</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FUR</td>
<td>MP</td>
<td>FUR</td>
</tr>
<tr>
<td>Repeatability (%R.SD)*</td>
<td>0.26</td>
<td>0.12</td>
<td>0.26</td>
</tr>
<tr>
<td>Repeatability area (%R.SD)*</td>
<td>0.16</td>
<td>0.32</td>
<td>0.16</td>
</tr>
<tr>
<td>Number of theoretical plates</td>
<td>2 499</td>
<td>7 892</td>
<td>2 499</td>
</tr>
<tr>
<td>Resolution*</td>
<td>1.57</td>
<td>12.49</td>
<td>1.57</td>
</tr>
<tr>
<td>Tailing factor*</td>
<td>1.18</td>
<td>1.09</td>
<td>1.18</td>
</tr>
<tr>
<td>Precision (%R.SD)†</td>
<td>3.55</td>
<td>3.54</td>
<td>2.13</td>
</tr>
<tr>
<td>Linearity (correlation coefficient)‡</td>
<td>0.9990</td>
<td>1.0000</td>
<td>0.9990</td>
</tr>
<tr>
<td>Accuracy recovery (%)†</td>
<td>103.48</td>
<td>104.35</td>
<td>100.83</td>
</tr>
<tr>
<td>Accuracy (%R.SD)†</td>
<td>0.61</td>
<td>0.36</td>
<td>1.75</td>
</tr>
<tr>
<td>Selectivity</td>
<td>No interference</td>
<td>No interference</td>
<td>No interference</td>
</tr>
</tbody>
</table>

*The results are the arithmetic means of six injections.
†Six samples, three injections of each sample.
‡At 40, 50, 80, 100, 120 and 150% concentration levels.
FUR, furosemide; FUR X, formulations with various excipients; MP, methylparaben; %R.SD, relative SD in %.
glass bottles: two for storage at room temperature (25°C±3°C), and two for storage at 40°C±0.5°C (i.e., four samples for each of the experimental conditions). The samples were protected from light.

The concentration of FUR and MP in the samples was estimated at the start of the stability study (c₀ = day of solution preparation, an initial content of 100%) and then at the time intervals of 7, 30, 90, 180 and 270 days. Each sample was measured in triplicate.

**Measurement of pH value**

The pH value was measured under stabilised conditions using a pH metre (pH 212 Microprocessor pH Metre, Hanna Instruments, Germany) with a combined pH electrode. Each sample was measured at the time intervals mentioned above.

**Efficacy of antimicrobial preservation**

The test of the antimicrobial activity of the preservative MP 0.1% w/v (Ph. Eur., 5.1.3), which consists of challenging the preparation with a prescribed inoculum of micro-organisms, was carried out at an accredited laboratory (ITEST plus, Hradec Kralove, Czech Republic).

**Data analysis**

At each time interval, the percentage of the initial concentration remaining was calculated for FUR and MP (n=4). Stability was defined as the retention of at least 90% and/or 80% of the initial concentration of FUR and/or MP, respectively.

**RESULTS**

Compositions of the preparations F1 and F2 are shown in table 1. Both formulations contained saccharine sodium 0.1% w/v as a taste modifier. They were prepared as quickly as possible to prevent decomposition of FUR by light.

In figure 1, the HPLC chromatogram showing the separation of standard solution 50 µg/mL of FUR and formulation F2 is illustrated; the results of method validation are summarised in table 2.

In tables 3 and 4, the mean value of percentage concentration ± SD of the initial FUR and the antimicrobial agent MP, respectively, in preparations F1 and F2 (n=4) are shown for the stability time points and conditions mentioned in the ‘Methods’ section. The amount of FUR and MP in milligrams per millilitre at the beginning of the study (c₀ = 100%) is given in the first row.

As illustrated in table 3, the FUR concentration remaining was higher than 91% after 270 days in both formulations F1 and F2 stored at both storage conditions (25°C and 40°C). The remaining MP concentration was higher than 80% after 270 days in both formulations stored at 25°C and in the formulation F1 stored at 40°C as shown in table 4. In all cases, the chromatograms showed no evidence of product degradation throughout the 9-month stability study. No detectable changes in colour, odour or taste were observed in either FUR formulation.

In contrast, a significant decrease in MP concentration in formulation F2 stored at 40°C was seen. The percentage of MP remained within ±11% for 30 days, decreasing to approximately 70% of the initial content after 90 days. At the end of the stability study (270 days), only approximately 40% of MP remained (table 4). Nevertheless, no apparent changes in colour, odour or taste were observed.

The value of pH for formulations F1 and F2 under the conditions of stability testing mentioned above was measured. The pH 6.6 and 7.5 for F1 and F2, respectively, remained practically unchanged throughout storage at room temperature and for F2 at 40°C; in preparation F1, the pH value declined slightly to 6.1 after 270 days when stored at 40°C.

**DISCUSSION**

FUR is an active compound traditionally used in paediatric cardiology. In paediatrics, oral liquid preparations, particularly solutions, are the best dosage forms for flexible and accurate dosing and compliance of patients. However, no commercially

| Table 3 Stability of furosemide in formulations F1 and F2 stored at 25°C and at 40°C* |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Time (days)                         | 25°C±3°C         | 40°C±0.5°C       | 25°C±3°C         | 40°C±0.5°C       |
| F1                                  | 2.15±0.02 mg/mL  | 2.12±0.05 mg/mL  | 2.15±0.02 mg/mL  | 2.12±0.05 mg/mL  |
| F2                                  | 99.06±2.35       | 94.34±1.77       | 99.06±2.35       | 94.34±1.77       |

*Mean ± SD of determinations for four samples (n=4).

| Table 4 Stability of methylparaben in formulations F1 and F2 stored at 25°C and at 40°C* |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Time (days)                         | 25°C±3°C         | 40°C±0.5°C       | 25°C±3°C         | 40°C±0.5°C       |
| F1                                  | 1.03±0.03 mg/mL  | 1.04±0.02 mg/mL  | 1.03±0.03 mg/mL  | 1.04±0.02 mg/mL  |
| F2                                  | 98.06±2.80       | 98.06±2.20       | 98.06±2.80       | 98.06±2.20       |

*Mean ± SD of determinations for four samples (n=4).
available liquid preparation is available that follows the latest recommendations on safety of paediatric drugs for the excipients used. FUR is practically insoluble in water, which is the main complication when preparing aqueous solutions. To increase the solubility of FUR in water, ethanol is often used in commercial preparations.\(^{1-3}\) Unfortunately, preparations containing ethanol cannot be recommended for use in paediatric patients. The formation of a FUR sodium salt by adjusting the alkaline pH is another method of making FUR soluble in water and is generally achieved with an aqueous solution of sodium hydroxide. A FUR injection solution whose pH value is approximately 9 is the example. In pharmacy, the commercially available aqueous injection can be simply diluted by WFI to achieve a FUR concentration suitable for paediatric patients—for example, 2 mg/mL. Apart from the mentioned high pH value, such an extemporaneously prepared oral solution has an unpleasant taste due to the presence of sodium hydroxide.

According to the requirements of the Pharmacopoeia, multidose liquid preparations must be protected from microbial contamination by addition of a suitable preservative.\(^{16}\) Unfortunately, widely used preservatives, such as sodium benzoate or potassium sorbate, have scarcely any antibacterial activity at an alkaline pH value. On the other hand, the paraben group of preservatives is effective over a wide pH range of 4–8 having an alkaline pH value. On the other hand, the paraben group of preservatives, such as sodium benzoate and butylparabens, neither MP nor ethylparaben showed any toxic effects on male reproductive organs, sperm parameters or sex hormones in juvenile rats.\(^{19}\) Therefore, and also owing to its higher solubility, MP was finally chosen as a preservative.

To improve palatability of the oral solution, addition of a suitable sweetener is usually necessary. Sucrose is often used in most paediatric liquid preparations and it was also tested during FUR formulation development. Unfortunately, we observed two main disadvantages: first, the pH value decreased to approximately 6, leading to the risk of FUR decomposition and/or precipitation; second, the colour of the solution changed to yellow or light brown during storage. HPLC showed that the stability of sucrose-containing solutions was only 90 days at room temperature (data not shown in this article). Finally, sodium saccharine 0.1% w/v was used in both formulations presented in this work (F1, F2) owing to its better stability.

**Developed paediatric formulations**

Two preparations of FUR (table 1) were formulated for extemporaneous preparation in a hospital or community pharmacy. Composition F1 was prepared by dissolving FUR in an appropriate volume of 1% sodium hydroxide solution, in a similar way to the large-scale manufacture of FUR injections. The volume of hydroxide solution added was determined by observing the dissolution visually. The final pH value of the F1 preparation was 6.6. The preparation is similar to simple dilution of a parenteral injection; however, the presence of hydroxide makes its taste unpleasant and a sweetener (sodium saccharine 0.1% w/v) was therefore used to improve palatability.

In formulation F2, the alkaline pH necessary for FUR dissolution in water was reached by addition of disodium hydrogen phosphate dodecahydrate, which has been successfully used also in previous paediatric propranolol and sotalol liquid formulations.\(^{20-22}\) The amount of disodium hydrogen phosphate dodecahydrate was adjusted experimentally during the preparation development. In our experience, this formulation has a more pleasant taste than the F1 formulation.

In the stability study, two batches of the formulated FUR aqueous solutions F1 and F2 were prepared in the Motol hospital pharmacy and stored in tightly closed amber glass bottles at 25°C±3°C and 40°C±0.5°C. The concentration of FUR and the preservative MP was estimated using HPLC for a period of 0–270 days. The level of FUR in mg/mL at the time of preparation was considered to be the initial concentration \((c_i=100\%)\). As can be seen in table 3, the FUR percentage content remained within the target limit of the initial concentration in both formulations throughout the 270-day storage period at room temperature. Both preparations had suitable pH for maintaining FUR solubility.

The concentration of MP remained within ±20% of the initial concentration for both solutions stored at room temperature and at 40°C for F1 for 9 months. On the contrary, a significant decrease in concentration was observed for MP in formulation F2 stored at 40°C, probably due to its decomposition. For F2, as shown in table 4, the target remaining concentration of ≥80% was maintained only up to 30 days.

Preparations F1 and F2 should be packaged in a brown glass container to protect from light. A screw cap suitable for use with a graduated pipette for oral use to achieve accurate dosing is recommended.

**CONCLUSIONS**

Two aqueous, ethanol-free oral solutions containing FUR at a concentration of 2 mg/mL were developed in accordance with the recent requirements for the safety of paediatric drugs. The preparations formulated for easy extemporaneous compounding in a pharmacy are suitable for the treatment of oedema therapy of various causes and for hypertension in paediatric groups aged >1 month. The excipients used ensured stable pH, antimicrobial stability and a pleasant taste. A 9-month stability study performed by validated HPLC analysis showed that the concentration of FUR in both F1 and F2 formulations was in accordance with the criterion that at least 90% of the initial content should remain during storage at 25°C or 40°C.

Nevertheless, preparation F1, which has a worse, slightly burning taste caused by the presence of sodium hydroxide, although a sweetener sodium saccharine 0.1% w/v was added, is less preferable than F2, which contains disodium hydrogen phosphate dodecahydrate. Moreover, sodium hydroxide is highly caustic and readily absorbs moisture and carbon dioxide from the air, making its manipulation difficult and routine preparation of its solution inconvenient in a pharmacy. On the other hand, preparation F2 has a more pleasant taste and is easier to prepare in a pharmacy as disodium hydrogen phosphate is easier to manipulate and weigh than sodium hydroxide. Formulation F2 therefore represents a compromise between good FUR solubility in water, taste acceptance in paediatric patients and fast compounding procedure. For long stability at room temperature, the stock F2 solution could be...
What this paper adds

What is already known about this subject
► Ethanol is widely used in registered furosemide (FUR) oral preparations to improve its solubility. However, ethanol is not a suitable excipient for preparations intended for use in paediatrics.
► If a marketed paediatric product is not available, extemporaneous preparation of a stable pharmaceutical product in a pharmacy has an essential role in the treatment of children.

What this study adds
► The stability of FUR in disodium hydrogen phosphate dodecahydrate aqueous solution in the presence of methylparaben is not known.
► Two developed formulations of FUR ethanol-free oral solution for use in infants were proposed for easy extemporaneous compounding in pharmacies. Stability for 270 days under room storage temperature was demonstrated by high-performance liquid chromatography analytical assay and pH measurement.
► The preparation containing disodium hydrogen phosphate dodecahydrate to reach the alkaline pH necessary for FUR dissolution in water is easier to prepare in routine practice and has a more pleasant taste than that prepared with sodium hydroxide.
► The preparations proposed offer personalisation of child therapy, reflecting the actual need.

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