

Hospital preparations of ethanol-free furosemide oral solutions: Formulation and stability study

Charles Bavouma Sombié^{1,2},
J. E. Kéré Guetambaba¹,
Hermine Zimé Diawara¹, Josias
Yaméogo¹, Salfo Ouédraogo¹,
Jonathan Goole³, Rasmané Semdé¹

¹Laboratory of Drug Development,
Doctoral School of Sciences and
Health, University Joseph KI-ZERBO,
03 BP 7021 Ouagadougou 03, ²Centre
hospitalier Universitaire Pédiatrique
Charles de Gaulle, Ouagadougou,
Burkina Faso, ³Unit of pharmaceuticals
and Biopharmaceutics, Université Libre
de Bruxelles, Boulevard du Triomphe,
Bruxelles, Belgique

J. Adv. Pharm. Technol. Res.

ABSTRACT

Furosemide is a diuretic frequently used in the therapeutic management of edema associated with cardiac, renal, and hepatic failure and hypertension. However, there are a very low number of pharmaceutical dosage forms containing furosemide that are suitable for children under 6- years old. Therefore, there is a real need to develop hospital preparations, especially in the hospital. Four oral pediatric solutions of furosemide (2 mg/MI) were formulated. Two of those solutions did not contain ethanol. For each formulation, 12 batches of 1600.0 MI were prepared and packaged in 250.0 MI brown glass bottles with polypropylene screw caps. The physicochemical properties (visual appearance, pH, osmolarity, drug content) and microbiological quality of the finished product were determined on the freshly prepared solutions and after 90 days of storage at 30°C/65% RH. The physicochemical and microbiological characteristics of the freshly prepared solutions were within the prescribed specifications. After 90 days of storage at 30°C/65% RH, the solutions containing sucrose and those without ethanol showed a slight decrease in pH and furosemide content of about 2.5%–4.5% (w/w). Despite this slight decrease, the characteristics remained within the prescribed specifications. Based on the stability profile of the ethanol-free solution containing sorbitol, it could be implemented in hospitals for the care of pediatric patients.

Key words: Alcohol, edema, furosemide, pediatric patients, solution

INTRODUCTION

Furosemide is a potent loop of Henle diuretic drug used in pediatrics for the treatment of edemas from cardiac, hepatic, and pulmonary origin and for nephrotic syndromes.^[1,2] It is usually marketed as tablets, capsules, and injectable solutions. The few available and marketed oral

liquids are found in Europe such as FRUSOL[®] (Rosemont Pharmaceuticals Ltd, UK), LASILIX[®] (Sanofi-Aventis, France), and IMPUGAN[®], (Balkanpharma Troyan AD, Bulgaria).^[3] These oral liquid dosages, in view of the low economic interest forms^[4] are not marketed in some developing countries. Access to this treatment for children under 6 years old is, therefore, very limited in these countries. The scarcity of pediatric medicines with marketing authorization is also observed in many pediatric diseases.^[5] This situation often leads to difficulties in the therapeutic management of some young patients in hospitals. To bypass the unavailability of pediatric medicines, clinicians often prescribe hospital formulations, leaving hospital pharmacists with the challenge to prepare extemporaneous oral solutions from

Address for correspondence:

Dr. Charles Bavouma Sombié,
Laboratory of Drug Development, Doctoral School of
Sciences and Health, University Joseph KI-ZERBO, 03 BP 7021
Ouagadougou 03, Centre hospitalier Universitaire Pédiatrique
Charles de Gaulle, Ouagadougou, Burkina Faso.
E-mail: charlsombie@yahoo.fr

Submitted: 15-Nov-2021

Accepted: 05-Mar-2022

Published: 07-Apr-2022

Access this article online

Quick Response Code:



Website:

www.japtr.org

DOI:

10.4103/japtr.japtr_325_21

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How to cite this article: Sombié CB, Guetambaba JE, Diawara HZ, Yaméogo J, Ouédraogo S, Goole J, *et al.* Hospital preparations of ethanol-free furosemide oral solutions: Formulation and stability study. *J Adv Pharm Technol Res* 2022;13:128-32.

commercially available, such as tablets or capsules.^[6-8] This method of preparation and administration may lead to a decreased therapeutic efficacy and a poor compliance for the patients.^[9] To improve access to certain pediatric dosage forms, the production of stable hospital preparations is necessary.^[10,11] Therefore, some studies have focused on the formulation of hospital compounding preparations of oral furosemide. For instance, furosemide suspensions have been developed from tablets^[12,13] or from the raw powder of the drug itself.^[3] However, the main difficulties encountered with furosemide-containing suspensions and solutions are respectively instability issues such as sedimentation and crystal growth observed during storage^[13,14] and pH value outside the stability range of furosemide.^[15] Some oral solutions of furosemide have been prepared.^[3,16] However, these preparations, as well as the few available commercial oral solutions of furosemide, contained ethanol. Ethanol may cause neurotoxicity and cardiovascular issues in the pediatric population and it is potentially dangerous in newborns. Its use in pharmaceutical preparations is regulated with maximum permissible limits that have been set for children under 6 years of age at <0.5% v/v and, in some countries, alcohol-free medicines are only allowed.^[17] In view of the regulatory requirements concerning the ethanol concentration in pediatric preparations, it is necessary to develop compounding preparations of ethanol-free oral solutions.

The present study was initiated with the aim to improve the availability of such dosage forms in hospitals. Thus, ethanol-free formulations of furosemide oral solutions were developed and their physicochemical and microbiological characteristics were evaluated.

MATERIALS AND METHODS

Furosemide was purchased from Fac Secundum Artem (Belgium). Ethanol (Carlo erba reagents, France), Glycerol (Fagron, Belgium), Sorbitol (ABC-Chemicals, Belgium), Sucrose (SN/SOSUCO, Burkina Faso), Methyl parahydroxybenzoate and Propyl parahydroxybenzoate (Sigma-Aldrich, USA), Strawberry Aroma (Nouvelle Parfumerie Gandour, Senegal), Sodium Hydroxide (VWR Chemicals, Belgium) and freshly prepared distilled water from the laboratory were used as excipients. The 250.0 ML brown glass (Type 2) vials with a polypropylene tamper-evident screw cap were sourced from Shanghai Best China Industry Co (China).

Formulation and preparation of furosemide oral solutions

Four formulations of furosemide oral solutions (2 mg/ML) were studied [Table 1]. These formulations are described as follows: S_{Sac} (formulated with sucrose without ethanol), S_{Sac+et} (formulated with sucrose and ethanol), S_{Sor} (formulated with sorbitol without ethanol), and S_{Sor+et} (formulated with sorbitol and ethanol).

Table 1: Qualitative and quantitative formulation of furosemide oral solutions

Component	Quantity			
	S_{Sac}	S_{Sor}	S_{Sac+et}	S_{Sor+et}
Furosemide (mg)	500.0	500.0	500.0	500.0
Alcohol (ML)	-	-	6.15	6.15
Sucrose (G)	100.0	-	100.0	-
Sorbitol (G)	-	75.0	-	75.0
Glycerol (ML)	25.0	25.0	25.0	25.0
Strawberry aroma (ML)	1.25	1.25	1.25	1.25
Parabens (G)	0.25	0.25	0.25	0.25
Sodium hydroxide 5N (qsp pH)	8.0	8.0	8.0	8.0
Purified water (ML) (qsp)	250.0	250.0	250.0	250.0

Three batches of 1600.0 ML of each solution were prepared as follow:

Preparation of ethanol-containing oral solution of furosemide

Furosemide powder was dispersed in 40.0 ML of alcohol in a 2.0 L beaker, and a few drops of NaOH (5N) were added under magnetic stirring. Then, the prescribed amounts of syrup A (500.0 ML of water, 1.6 G of parabens, and 640.0 G of sucrose) or B (500.0 ML of water, 1.6 G of parabens, and 480.0 G of sorbitol), glycerol, aroma distilled water were added. The resulting mixture was stirred at 50°C, 600 rpm for 10 min. The pH of the solution was measured and adjusted to pH 8 using with NaOH (5N). The resulting bulk solution was filtered through a nylon sieve 40 mesh and dispensed into brown glass vials.

Preparation of ethanol-free oral solution of furosemide.

They were prepared as described above. However, the alcohol was replaced by distilled water.

Physicochemical and microbiological quality control

Organoleptic properties

The color, appearance, and taste of the different furosemide oral solutions were visually evaluated.

Measurement of pH and osmolality

The pH was determined with the WTW pH meter 310 (Germany) at 25°C. The osmolality of solutions previously diluted to 1/10 was determined with the Micro-osmometer Type 6 (Germany). The tests were carried out on each batch and were performed in triplicate. The mean (M) and standard deviation (SD) were calculated ($M \pm SD$, $n = 3$).

Assay of furosemide

The ultraviolet (UV) spectrophotometric assay method used for the determination of furosemide concentrations in injectable solutions described in the British Pharmacopoeia 2020,^[18] was adapted to quantify furosemide in oral

solutions. The UV-visible spectrophotometer, Evolution 60S (Thermo Fisher Scientific Inc., France) was used. The absorbance was corrected by determining the absorbance of the vehicle consisting of the solution without furosemide. The content of furosemide in the solutions was expressed as a percentage (% w/w).

Microbiological contamination

The microbiological quality control in accordance with the European Pharmacopoeia^[19] was used.

Stability study

The solutions were stored at 30°C/65% RH in a Memmert climate chamber ICH 260 (Germany) for 90 days. The physicochemical and microbiological quality were monitored as previously described immediately in preparation (D0) and after 30 (D30), 60 (D60), and 90 days (D90).

RESULTS

Formulation

Formulations of the different solutions are described in Table 1.

Physicochemical and microbiological quality control

Furosemide oral solutions were light pink (Sorbitol solution) and brown (sucrose solution). The concentration of furosemide in the freshly prepared solution was 103.8 ± 0.7 (SSac), 100.6 ± 0.4 (SSac + et), 103.1 ± 0.5 (SSor), 99.5 ± 0.8 (SSor + et). The pH values of the freshly prepared solutions varied between 8.2 and 8.4. The osmolality of the fresh oral solutions was around 2500.0 mOsm/kg for the sucrose-containing oral solutions and 3000.0 mOsm/kg for the sorbitol-containing oral solutions [Table 2]. No aerobic micro-organisms, yeasts, molds, and the specific objectionable bacteria (*Escherichia coli*) were found in the freshly prepared solutions.

Stability study

The pH, osmolality, and concentration of furosemide slightly varied during the stability study but were within the prescribed specifications [Table 2]. A decrease in the concentration of furosemide of approximately 4.4% w/w for SSac, 2.5% w/w for SSac + et, 2.6% w/w for SSor and 0.5% w/w for SSor + et, was observed after 90 days of storage at 30°C/65° RH. Bacterial or fungal growth was not found.

DISCUSSION

The concentration of furosemide in the solutions (2 mg/ml) was lower than that of LASILIX® oral solution (10 mg/ml) but similar to that of hospital preparations previously described in the literature.^[3,12] Oral furosemide solution is usually administered for pediatric patients 1–3 mg/kg body weight daily.^[1,2] The amount of other components in the preparation

Table 2: Evolution of physicochemical parameters (mean±standard deviation, n=3) of oral solutions of furosemide stored at 30°C/65% RH for 90 days

Days	Assay (% w/w)				pH				Osmolality (mOsm/kg)				
	S _{Sac}	S _{Sac+et}	S _{Sor}	S _{Sor+et}	S _{Sac-tet}	S _{Sor}	S _{Sor+et}	S _{Sac}	S _{Sac-tet}	S _{Sor}	S _{Sor+et}	S _{Sac-tet}	S _{Sor+et}
0	103.8±0.7	100.6±0.4	103.1±0.5	99.5±0.8	8.2±0.1	8.4±0.1	8.4±0.1	2540.0±10.0	2613±104.0	2745.0±225.0	3025.0±175.0	2613±104.0	2745.0±225.0
30	102.0±0.6	99.7±0.2	102.0±0.6	100.0±0.8	8.1±0.0	8.2±0.0	8.3±0.0	2610.0±75.0	2699±100.0	2755.0±66.0	3102.0±95.0	2699±100.0	2755.0±66.0
60	100.9±0.3	97.3±0.6	100.2±0.9	99.5±0.5	7.8±0.1	7.8±0.0	8.0±0.0	2668.0±64.0	2758±86.0	2783.0±56.0	3235.0±188.0	2758±86.0	2783.0±56.0
90	99.4±0.4	97.5±0.4	100.5±0.9	99.0±0.5	7.6±0.0	7.8±0.0	7.8±0.0	2660.0±76.0	2700±18.0	2753.0±98.0	3200.0±105.0	2700±18.0	2753.0±98.0

RH: Relative Humidity

were determined according to the recommendations of the handbook of pharmaceutical excipients.^[20] Sorbitol or maltitol are the main sweeteners regularly used in furosemide oral solutions.^[2,16] However, in this study, the alternative use of another sweetener such as sucrose was also evaluated. The use of antimicrobial preservatives was in accordance with the recommendations for multidose oral preparations. The use of parabens was preferred due to their compatibility with the other components and to their suitable pH spectrum of activity (pH 4.0–8.0).^[20] Acceptable daily intake for parabens is 10 mg/kg body weight/day.^[21] While the use of parabens in formulations for children is generally tolerated,^[7] it is usually not recommended neonatal patient care.^[17,21] Indeed, the binding of both methyl and propyl-paraben to albumin is well documented. Furthermore, methylparaben displaces bilirubin from albumin and can cause kernicterus.^[22] Alcohol was used as a cosolvent in two of the four vehicles. Sodium hydroxide 5N was used as a solubilizing agent and pH adjuster in the different solutions.

The assay of furosemide in the freshly prepared solution was within the British Pharmacopeia 2020 specification (95%–105% w/w). The pH values of freshly prepared solutions were within the USP 41 specifications (pH = 7.0–10.0) for oral solutions of furosemide [Table 2]. However, they were higher than the pH of the ethanol-free furosemide solution of Zahálka *et al.* in 2017 (pH = 6.6). Furosemide is unstable in acid media and has been shown to undergo acid-catalyzed hydrolysis in aqueous solution to yield 4-chloro-5-sulfamoylanthranilic acid and furfuryl alcohol.^[23] In contrast, alkaline solutions of furosemide elicit higher stability.^[24] Therefore, it was important to keep it within its stability range, especially at pH values >7.0,^[15] hence the choice in our study to set the pH at 8.0. However, higher alkalinity may reduce patient compliance due to its taste. Therefore, it is usually recommended to shade the unpleasant taste by various sweeteners and flavors.

The osmolality of the oral solutions varied depending on the used sweetener; with measured values of 2500.0 mOsm/kg for sucrose-containing oral solutions and 3000.0 mOsm/kg for sorbitol-containing oral solutions. They were similar to that of hospital preparation of furosemide syrup from HUG (3000.0 mOsm/kg).^[16] Osmolality is an important parameter for oral preparations intended for use in children. The stomach can tolerate an osmolality of up to 450 mOsm/kg.^[16] Oral bolus administration of drugs with an osmolality > 1000.0 mOsm/kg can lead to pyloric constriction and cause nausea, vomiting, and cramps (delayed gastric emptying). However, despite the aforementioned side effects, therapeutic preparations with osmolality above 6000.0 mOsm/kg intended for children, are found on the market.^[25] To compensate for the high osmolality of liquid oral preparations, it is recommended to administer these

preparations after meals or in the alternative, to dilute them with high volumes of water.^[16]

The microbiological quality of the prepared solutions was in accordance with the specifications for liquid oral forms recorded in the European Pharmacopoeia 10th Edition. The manufacturing process and conditions did not expose the solutions to possible microbiological contamination.

After 90 days of storage at 30°C/65°RH, a decrease in furosemide content of at least 4.4% w/w and 2.6% was observed with sucrose and sorbitol, respectively. Similar findings were previously made in the evaluating the stability of furosemide in different aqueous solutions (e.g., sucrose, sorbitol solution, and glycerin solutions) stored at 65°C for 21 days.^[24] In addition to the temperature, the presence of other excipients would seem to influence the stability of furosemide. This would seem in accordance with the finding that ethanol-containing solutions showed a more stable furosemide content profile, as compared to ethanol-free solutions. This phenomenon was more pronounced for sorbitol-containing solutions and was consistent with literature recorded data.^[24] Ethanol, therefore, seems to have a stabilizing effect on the preparation.^[24] Furthermore, a decrease in furosemide content was also observed in suspensions stored at 30°C ± 2°C for 60 days^[13] and oral solutions stored at 25°±3°C for 270 days.^[3] However, despite the decrease in the furosemide content in our different preparations, it remained within the specifications of pharmacopeia. The pH of the furosemide solutions decreased during storage but remained within the USP specifications. The decrease in pH was also observed in other furosemide solutions during storage.^[24] This decrease is thought to derive from the formation of 4-chloro-5-sulfamo-yl-anthranilic acid resulting from the hydrolysis of furosemide in aqueous medium.^[23,24] The decrease in pH correlates with the decrease in furosemide concentration. Despite a slight decrease in pH and furosemide content, organoleptic characteristics and osmolality did not change over time.

Finally, bacterial or fungal growth was not found in the preparations neither in the freshly prepared solutions nor after storage. The microbiological quality of the different oral solutions remained consistent during the stability study.

CONCLUSION

Preparations of furosemide oral solutions were carried out from formulations involving various excipients including sorbitol or sucrose, ethanol, and parabens. The qualitative composition was similar to that of pharmaceutical products such as LASILIX[®] oral solution. The presence or absence of ethanol in the solutions had no major influence on the stability after 90 days of storage. The solutions containing

sorbitol had the best stability profiles and could therefore be used in hospitals.

Financial support and sponsorship

Académie de recherche Sud (Belgique) and Centre d'Excellence Africaine, Centre de formation, de recherche et d'expertise en sciences du médicament of Université Joseph KI-ZERBO (Burkina Faso).

Conflicts of interest

There are no conflicts of interest.

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