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Research Article

Solubility, pH and Temperature are Critical Parameters of Furosemide in Elastomeric Pump Infusion: Solving a Problem for Clinical Employment

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Abstract

Objective: To determine the furosemide infusion availability considering several critical physical parameters.

Methods: The filling protocol has been carried out in U.Ma.Ca., Hospital Pharmacy Unit of Bari (Italy), for furosemide in elastomeric pump. The qualitative and qualitative aspect have been monitored with HPLC.

Results: This innovative protocol permits to have a stable infusing concentration of furosemide without precipitation.

Conclusion: Both the filling developed method and the protocol to monitor qualitative and quantitative furosemide infusing concentration with elastomeric pump are suggested as guidelines for clinical employment.

Keywords: Elastomeric pump; Furosemide; HPLC; pH; Solubility

Introduction

The Heart Failure (HF) is a strong problem among the elderly. The treatment of HF with furosemide is the gold standard but conversely several aspects such as intravenous infusion leads to hospitalization Furosemide is sparsely employed in elastomeric infusion pumps although it could be an alternative treatment for HF. Specific protocol for s.c. furosemide treatment, could lead to treat ambulatory patients with decompensated HF. The setting of several parameters (pH, temperature and concentration) is fundamental for this treatment and aim of present study is to carry out a protocol listing major details for employing furosemide in elastomeric pump devoid of side effects.

In this study we tested furosemide in infusion medical device although the most important problem due to this therapeutic strategy leads to block the infusion for precipitation into the line of medical device because the compound has low solubility and the pH and temperature could modify the concentration of drug that is infused. A qualitative/quantitative control of drug in medical device during the period of therapy has not reported to date. For this purpose, aim of this studies is to develop a safety filling protocol and a qualitative/quantitative evaluation of furosemide that is infused.

Furosemide infusion with elastomeric pump present several problems in term of solubility, pH and temperature The purpose of this study is to verify the stability of Furosemide into the Myfuser® disposable pump (F 0020S, 2.0 mL/h in 60 mL, manufactured by Canox M.D. Srl, Trieste, Italy) in Normal Saline (NS), at storage periods and temperatures similar to those the drug is usually prepared and stored in Pharmacies and Hospitals for administration to patients. This study is carried out in collaboration with the Unit of Antineoplastic Drug Handling (U.Ma.CA.) at the Cancer Institute

"Giovanni Paolo II" (Bari). In particular, Furosemide 5 mg/mL in NS (250 mg/25 mL of Furosemide + 25 mL NS) has been studied in the Myfuser® pump and the studies were performed at 25°C for 0 h,12 h, and 48h.

According to the scientific literature [1,2], Furosemide is reported to be an "almost insoluble drug in water," with a "natural" solubility of 0.0731 mg/mL at 30°C at pH 7.0. In order to increase the drug concentration to clinically useful levels, the manufacturers add to the solution of the drug the excipient sodium hydroxide which increases the pH of the solution from initial value of 7.0 to a final value of 9.0 ca. (8.35-9.35) and thus allows to Furosemide to reach the final concentration of drug to 10 mg/mL at pH 9.0. In other terms, the addition of sodium hydroxide increases the initial poor solubility of Furosemide in water by 137 times ca., and this high factor anticipates that the final solution will present a limited stability, i.e. an even small decrease of pH will greatly affect the capacity of the drug to remain in solution.

Actually, the 2 initial tests performed on Myfuser pump presented a similar problem. For all tested times (0 h, 12 h, 48 h) at 25°C, while no peaks were detected due to the degradation of the drug and/or to medical device-drug interaction, instead after few hours from preparation of the pumps in the 1st test one pump presented a micro-precipitation of the drug and in the 2nd test the micro-precipitation appeared at the 48 hours control in one more pump. In fact, at 25°C it has been verified that the device flux after 2-3 hours was dramatically reduced due to precipitation of compound.

During the revision of the used protocol, it has been noticed that, during the filling phase of the pumps, in the 2 first tests, the 25 mL of NS had been added before the 25 mL of Furosemide. In the 3rd test, *vice versa*, this sequence had been inverted, starting first with Furosemide and then adding NS, with the result that no micro-precipitation occurred in both pumps.

For this reason, a specific protocol has been carried out as reported in (Table 1):

Drug	Volume	Filled concentration	Diluent	Brand
Furosemide	50 ml (25 mL of Furosemide + 25 mL NS)	5 mg/ml (pH = 8.68)	NS (pH 5.5)	Furosemide 250 mg/25 mL

Table 1: Preparation of Furosemide filled in disposable pump.

The mast of this study is the filling procedure developed in collaboration with the Unit of Antineoplastic Drug Handling (U.Ma.CA.) at the Cancer Institute "Giovanni Paolo II" (Bari). The manipulation was performed in accordance with international standard guidelines on injectables. In the pump the final concentration in C=5 mg/mL and the total volume is V=50 mL. The study was performed using two elastomeric pumps and NS as diluent. In all performed studies, the stability-indicating method involves the use of HPLC analysis, allowing the unambiguous assessment of drug purity, stability, and compatibility with medical devices. The part of the device that is in contact with the drug are the elastomeric membrane and the infusion plastic line at the moment of sampling [3-7].

Experimental section and Methodology

Medical device is Myfuser® pump F 0020S (2.0 mL/h flow and 60 mL volume); The experimental condition is summarized in (Table 2).

Concentration	5 mg/mL			
Diluent	NS			
Storage condition	25°C			
Determinations	0 h	12 h	24 h	48 h
Test solution pH (25°C)	7.02 ± 0.02			

Table 2. Experimental conditions.

The collection was carried out directly by the terminal part of the plastic infusion line in a tube and then the solution was transferred into vials for HPLC analysis. The sample was used after dilution in HPLC Analysis. HPLC Analyses were performed on a Shimadzu Prominence Modular HPLC equipped with System Controller CBM-20A, Photo-diode Array detector SPDM20A and controlled by LabSolutions WS-Single PDA (Vers. 5) WS Software. The employed column was a C18 reversed phase column Shim-pack VP-ODS 5 µm 250 mm x 4.6 mm. The determination of pH was carried out by a membrane pH meter Hanna instruments HI8314. All chemicals and reagents were of the highest purity. All solvents were HPLC grade quality and all chemicals were purchased from Honeywell Riedel-de-Haën.

Instrumental HPLC conditions

Wavelength: 254 nm: Flow: 1.0 mL/min; mobile phase: (CH3CN): (25 mm NaH2PO4 pH=3) = (65:35); injection volume: 100 µL; retention time: about 3.6 min; detector: DAD; column temperature: 25°C. The samples, taken on the indicated hours, were used after dilution for HPLC analysis. Furosemide qualitative and quantitative results have been compared with the data reported in literature about substance identification, drug shelf life, safety dose and degradation products.

Results

In this study the employed method involved the use of HPLC analysis and pH determination. The sample was taken over the studied period and submitted to HPLC analysis allowing the

unambiguous assessment of drug purity, stability, and compatibility. The used procedure for establishing purity and stability of the tested drug was to compare the HPLC results with that of a reference solution. For the qualitative evaluation the HPLC of the sample was compared with the results obtained with a standard solution of the drug. Moreover, particular attention was given to the monitoring of colour and clarity of the solution into the device and into the taken samples. For the quantitative evaluation, the area under the peak of interest was compared with that of a reference solution (t= 0 h) to evaluate the stability of drug concentration during the period of analysis. Final quantitative results are reported in term of "average concentration" and "% average concentration change" of samples considering the starting concentration measured at t=0 h. Quantitative analyses are performed by using the external standard method to construct a calibration curve (Figure 1) for the calculation of the concentrations. In (Table 3) the results obtained at 25°C for 0 h, 12 h, 24 h and 48 h are reported.

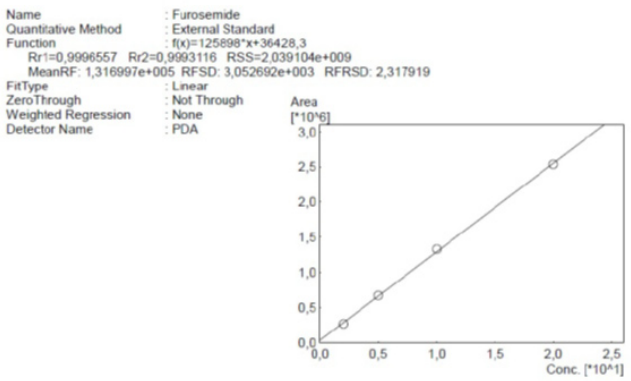


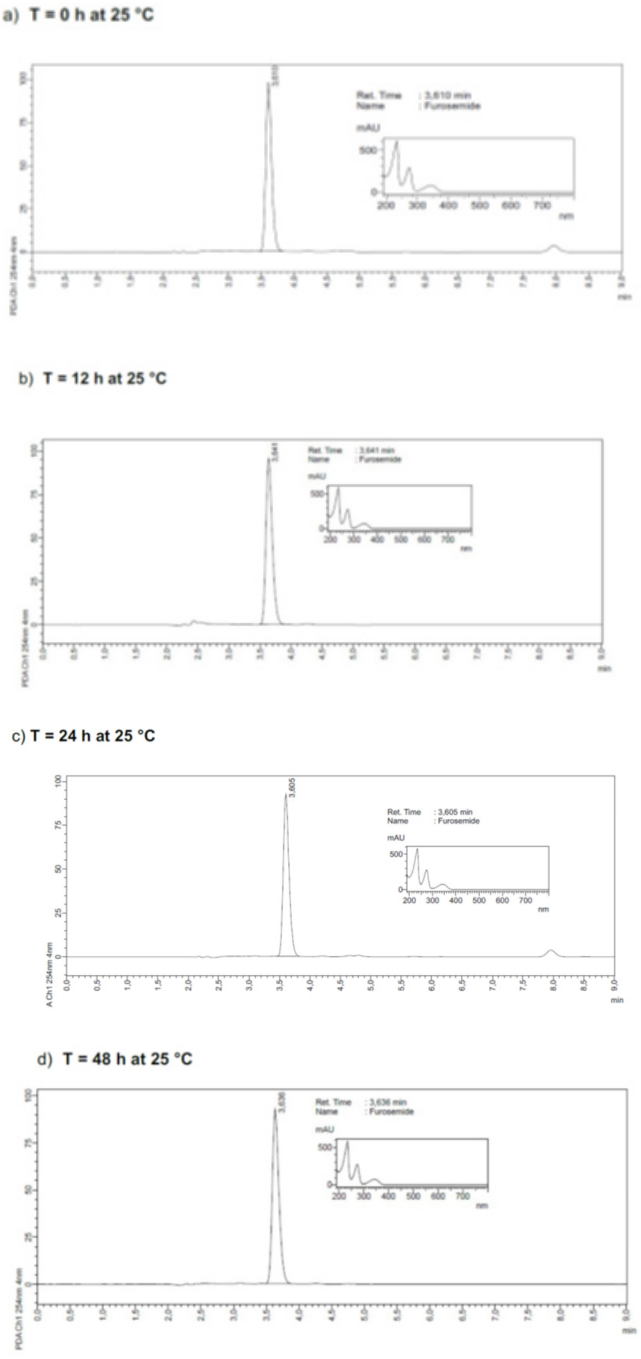
Figure 1: Representative calibration curve of Furosemide.

h	Mean concentration value (mg/mL)	Concentration Change (%)	pH value
0	4.57±0.03	0	7.10±0.05
12	4.55±0.04	-0.44	N. D.
24	4.55±0.05	-0.44	N. D.
48	4.51±0.07	-1.31	7.04±0.05

Table 3. Concentration of Furosemide at 25°C at each studied time point.

In terms of qualitative analysis is possible to verify that in the obtained HPLC chromatograms of Furosemide samples tested in Myfuser® device for all tested times (0 h, 12 h, 24 h, 48 h) at 25°C no peaks were detected due to the degradation of the drug and/or to medical device-drug interaction (Figures 2a-d).

In addition, the study of % variation of concentration has been employed to appreciate the stability of drug concentration during the requested period of observation. As reported in the (Table 3), after 12 h and 24 h a decrease in concentration of 0.44% was observed. After 48 h, a decrease in concentration of 1.31% was observed. The values are within the limits if the stability of Furosemide solution is defined as retention of at least 95% of the initial concentration.



Figures 2a-d: Representative chromatograms obtained by HPLC analysis of taken samples are reported in (Table 3).

Conclusion

This present study evaluated the criticisms of some parameters for administering 5 mg/mL Furosemide in medical device. The filling protocol and the control of concentration, pH, temperature and qualitative and quantitative aspect permit to suggest this protocol as guidelines for Furosemide administration with elastomeric pump.

Author Contribution

Colabufo NA, Leopoldo M carried out analysis with HPLC at the signed points.

Leonetti F handled the statistical parameters.

Nardulli P, Calabrò C suggested the optimization of filling protocol of medical devices meeting the guidelines of procedure.

Milani A is the producer (Canox SRL) of Medical devices and gave us the elastomers for all experiments

Conflict of Interest

For Colabufo NA, Leopoldo M, Leonetti F, Nardulli P, Calabrò C there is not conflict of interest.

Milani A is Head of Canox but he did not handle the data. He gave us the medical device for developing the innovative Furosemide filling and infusion protocol.

All experiments have been carried out only with medical devices without involved patients

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