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Original article

Comparative Study of Different Brands of Furosemide Injection

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ABSTRACT

Furosemide is one of loop diuretics which are very important drugs for treatment of hypertension and other medical problems. Parenteral furosemide is considered more effective than oral formulations; therefore, it is important to evaluate its therapeutic effectiveness starting from physicochemical properties. The aim of this study was to assess quality of five different brands of furosemide injection collected from different pharmacies in Tripoli-Libya. The five brands were tested for their alkalinity, ultraviolet wavelength maxima and content uniformity to assess if they comply with standards of BP2009. Manufacturing date was not printed in four samples. The pH of sample E was lower than accepted limit in addition to a low content of furosemide in sample D making it unacceptable. The results assured importance for parenteral products to comply with all physicochemical specifications as well as labelling. This would assure efficacy and safety of the drugs.

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INTRODUCTION

Furosemide is a loop diuretic which is used for the treatment of Hypertension, chronic congestive heart failure and edema associated with hepatic cirrhosis where furosemide increases water loss from the body [1,2]. Furosemide has a fast onset and short duration of action and has been used safely and effectively in both pediatric and adult patients [3]. Furosemide is administered orally or by parental route. There are many brands of furosemide IV injections. There are several methods of analysis for the estimation of Furosemide as raw material, in pharmaceutical formulations and in biological samples either alone or in combination with other drugs [4-7]. The literature reported the use of Uv spectroscopy, HPLC/MS/MS, capillary electrophoresis and FT-IR for detecting furosemide in different samples [8].

Furosemide is a chlorobenzoic acid that is 4-chlorobenzoic acid substituted by a (furan-2-ylmethyl)amino and a sulfamoyl group at position 2 and 5 respectively. Therefore, it is considered as a sulfonamide, a chlorobenzoic acid and a member of furans; figure 1 [9]. Its UV absorption is due to these functional groups especially conjugation of the double bonds and presence of many chromophores (highly electronegative atoms such as oxygen, chlorine and nitrogen atoms) [10].

Parenteral formulations must comply with many qualities control tests such as: content uniformity, extractable volume, pH, particulate matter in injections, bacterial endotoxin test, pyrogen test, sterility test [11]. This study was carried out to evaluate many brands of furosemide injection marketed in Tripoli-Libya using pharmacopoeia methods of analysis [12]. The tests included identification, clarity, volume pH and assay. The companies tested are listed in table 1.

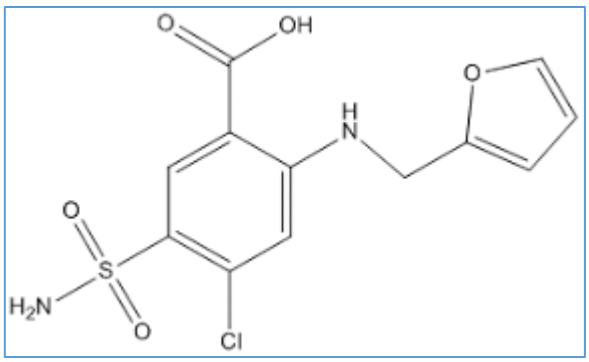

Figure 1. Chemical structure of furosemide.

Table 1. Different brands of furosemide injections tested.

No.	Sample	Origin/Source	Batch	Mg date	Exp date
1.	A	Albania	2322	Not printed	09/2026
2.	B	Turkey	A10159A	Not printed	02/2027
3.	C	Tunesia	22A0066	Not printed	02/2025
4.	D	Italy	M1545	Not printed	04/25
5.	E	India	GN729	11/2022	10/2025

MATERIALS AND METHODS

Materials

Sodium hydroxide was obtained from Sigma, UK. pH meter 350 was from Jenway, UK. UV spectrophotometer UV-31 Scan was from EU Designed, P.R.C.

Methods

Package and labelling

A visual inspection and listing different information on primary and secondary package were carried out.

Volume uniformity

Number of tested vials depends on the stated volume on each ampoule; table 2; [11]. Therefore, volumes were measured for 5 ampoules from each company using a syringe of suitable capacity.

Table 2: Number of vials tested according to content of vials.

Stated volume	Number of vials
< 3ml	5
3-10 ml	3
> 10ml	1

pH

The content of ampoules was tested for pH by direct measurement and listing observations. The results were compared to the range (8.0 – 9.3) [12].

Identification

The solution obtained from assay preparation was scanned between (220-320 nm). According to the pharmacopoieal specifications; this solution was expected to exhibit two maxima at 228nm and 271 nm [12].

Assay

To a volume containing 20mg of furosemide sufficient water was added to produce 100mL. 5 ml was taken and sufficient 0.1N NaOH was added up to 100ml. Absorbance was measured at 271nm taking 580 as A (15, 1cm) at 271nm [12].

RESULTS

Packaging and labelling

All ampoules were made of opaque glass which is appropriate for light-sensitive furosemide (and as directed by BP2009) [12]. Some of information on package was missing like production date, table 1. It was also noticed that some of information on the primary package were missing. Also, the brand obtained from India; product E; showed irregular break down of glass ampoules while opening with possibility of presence of broken glass within the ampoule prior to administration.

Volume uniformity

It was difficult to obtain whole volume from the ampoule unless withdrawn by syringe (exactly like administration). It was found that no more than two of the five tested ampoules were less than stated volume by not more than 0.1mL (2mL ± 0.1mL); no specifications within BP2009.

Alkalinity

Only Indian company (sample E) was less than pH range stated in BP2009 (measured pH =7.67).

Table 3. The list of pH values and absorption values for the different companies.

No.	Sample	Origin/ Source	pH	$\lambda_{max\ 1}$ (nm)	$\lambda_{max\ 2}$ (nm)	A (271nm)	% Content
1.	A	Albania	8.73	230	271	0.547	94.3 %
2.	B	Turkey	8.62	230	271	0.548	94.5 %
3.	C	Tunesia	8.52	225	271	0.597	103 %
4.	D	Italy	8.62	230	271	0.517	89.1 %
5.	E	India	7.67	230	271	0.614	105.8 %

Identification

According to BP2009, solution prepared for assay was expected to have two maxima at 228 and 271 nm; [12]. However, not all brands complied with these specifications; table 3 and figure 2. This would indicate instability or sensitivity of furosemide to light especially at 228 nm.

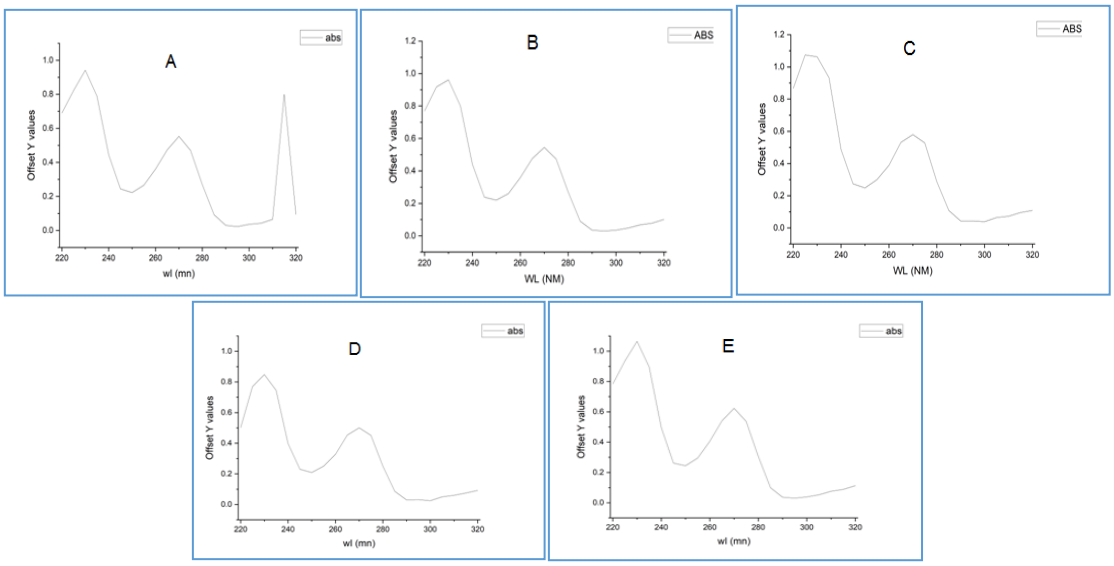

Figure 2: UV spectra of the five samples A-E.

Assay

Samples A and B were below the accepted limit by less than 1%. However, sample D had 89.1 % of API making it unacceptable although it had a maximum at 271 nm, table 2.

DISCUSSION

It should be noted that the drug is very sensitive to light and may have been degraded and therefore first maximum

absorption was at 230 nm instead of 228 nm. The exposure of aqueous furosemide solution to UV light could lead to photo-hydrolysis, which would give rise to a yellow solution containing the degradation products 4-chloro-5-sulfamoylanthranilyc acid (CSA) and and furfuryl alcohol (FA). These degradation compounds were formed due to the hydrolytic reaction which causes the oxidation of the bond between the secondary amine and the methylene moiety [13]. In addition to formation of dimers and polymers through hydrolysis, oxidation or polymerization processes [14]. This hydrolysis could lead to yellowish phenomena where the aqueous solution of furosemide turned to yellow when exposed to UV light for 1 hour or more which also led to broadening of absorption peaks [15].
Also, there was evidence that some of the products contained a lower amount of the drug; sample D; which would need more investigation. It was suggested to perform tests for each sample individually rather than preparing all samples together to avoid any possibility of being exposed to light for a longer time.

CONCLUSION

Furosemide is increasingly used for its diuretic properties as a first line treatment of edematous conditions associated with heart, kidney, and liver diseases. It is of vital importance to check on compatibility of its formulations with pharmacopoial specifications and excluding any possible degradation reactions while storing and administration. This will assure safety and cost-effectiveness of its products. Therefore; further investigations are required to assess different parameters of furosemide parenteral formulations.

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Conflicts of Interest
The authors declare that there are no financial, personal, or professional conflicts of interest to declare.

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دراسة مقارنة لشركات مختلفة لحقن الفيوروسيمايد

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المستخلص

يعتبر دواء الفيوروسيمايد نوع من أدوية المدرة للبول و التي تستعمل لعلاج ضغط الدم المرتفع و غيره من الأمراض. الحقن الوريدية للفيوروسيمايد هي الأكثر تأثيراً مقارنة بالمستحضرات الفموية و لذلك فإن من غاية الأهمية تقييم مدى فعاليته باجراء اختبارات فيزيائية و كيميائية. تهدف الدراسة لتقييم جودة خمسة منتجات دوائية لشركات مختلفة حيث تم تجميعها من صيدليات مختلفة بطرابلس – ليبيا. المنتجات الخمسة ثم اختبارهم من ناحية القاعدية، الامتصاص الطيفي للأشعة فوق البنفسجية، و تجانس المحتوى. و تقييم مدى مطابقتها مع مواصفات الدستور البريطاني. وجد أن تاريخ التصنيع لم يكن مكتوبا على ارلع منتجات. أيضا الرقم الهيدروجيني للعينة E كان أقل من المدى المذكور بالمرجع. وجد أن العينة D احتوت أقل كمية من الدواء و أقل من المطلوب مما جعلها مرفوضة . يجب أن تستوفي المنتجات الوريدية كامل المواصفات ابتداءا من الخصائص الفيزيائية الى المعلومات على المغلف و انتهاءا بمحتوى و تلركيز الدواء لضمان فعالية الدواء و ايضا عدم الضرر بصحة المريض.

الكلمات الدالة. فوروسيميد، حقنة، ضوء، امتصاص الأشعة فوق البنفسجية.