

## Chemical and biopharmaceutical assay of different brands of frusemide tablets

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### ABSTRACT

**Objective:** To evaluate the chemical and biopharmaceutical equivalence of frusemide tablets from different companies.

**Methods:** This study was conducted on five brands of frusemide tablets available in the pharmacies of Mosul city from different manufacturing companies. These brands have been evaluated using some quality control tests of uniformity of weight, hardness, disintegration time, dissolution rate determination for the tablets.

**Results:** The results obtained have been discussed in some detail using monographs in the United State Pharmacopeia (USP) and British Pharmacopeia (BP). All the brands content were within the acceptable range of USP (90-110 %), the disintegration time of all the brands also within the range of the USP and BP. The dissolution profile also were within the acceptable range of USP not less than 80% of the labeled amount of frusemide is dissolved in 60 minutes.

**Conclusion:** All the brands tested in this study may be used interchangeably.

**Keywords:** Bioequivalence, dissolution, disintegration, frusemide, quality control.

### الخلاصة

**الهدف:** تقييم التكافؤ الكيميائي والحيوي الصيدلاني لحبوب عقار فروسيميد من خمسة شركات مختلفة. **طرائق العمل:** أجريت هذه الدراسة على حبوب الفروسيميد المتوفرة في صيدليات مدينة الموصل و المصنعة في خمسة شركات مختلفة تم تقييمها باستخدام بعض مقاييس السيطرة النوعية مثل تماثل الوزن، الصلابة، زمن الانحلال، وسرعة الذوبان للحبوب.

**النتائج:** تم مقارنة النتائج مع ثوابت موجودة في دستور الأدوية الأمريكي والبريطاني وأثبتت أن المحتوى الدوائي لكل المنتجات هو ضمن الحدود المسموح بها طبقاً لدستور الأدوية الأمريكي (90-110 %) وكان زمن الانحلال لكل المنتجات مطابقاً لما موجود في دستور الأدوية الأمريكي والبريطاني. وكانت سرعة الذوبان أيضاً ضمن الحدود المطلوبة من قبل دستور الأدوية الأمريكي " يجب أن لا تقل كمية الفروسيميد الذائبة عن 80% خلال 60 دقيقة". **الاستنتاج:** كل المنتجات التي تم فحصها في هذه الدراسة يمكن أن تستخدم كبدايل لبعضها البعض.

Frusemide is one of the loop diuretics acts by inhibiting  $\text{Na}^+\text{-K}^+\text{-2Cl}^-$  symport in the thick ascending loop of henle. It is used primarily in the treatment of acute pulmonary edema and other edematous conditions and is widely used for the treatment of chronic congestive heart failure. Frusemide is also used for the management of hypercalcaemia, hyperkalemia and in some anion over dose such as bromide, fluoride and iodide. Frusemide is also used to increase the rate of urine flow and enhance  $\text{K}^+$  excretion in acute renal failure.

Because of this multiple uses of frusemide and the increase in the number of

prescriptions that contain this drug, which resulted in higher demand and the need to increase its supply has led to more importation while some indigenous pharmaceutical industries began to produce their own brands of frusemide.

Some of these brands or generic of frusemide is not bioequivalent to a reference product and need more investigation to assess their quality. For example, Elgindy et al evaluated five commercial brands of frusemide tablets using the official and non-official tests. These tests include: uniformity of weight, hardness, friability and disintegration time.

The results obtained showed that most of these brands failed to attain the USP requirements<sup>٧</sup>.

In vitro testing or quality control of drugs is a set of studies or experiments undertaken during production (in process) and occasionally ought to be undertaken post-production by regulatory agencies and researchers. Therefore, post-market surveillance or monitoring is very important for assessing the quality of drugs and to detect any substandard and counterfeit drug products.

Counterfeit and substandard medicines are a major cause of morbidity, mortality and loss of public confidence in drugs and health structures<sup>٤</sup>. China and India are known as the leading countries in counterfeit drugs production and also the

bulk active ingredients they produce are used for counterfeiting worldwide<sup>٥</sup>.

Generic substitution could be considered when a generic copy of a reference drug contain identical amounts of the same active ingredients in the same dose formulation and route of administration as well as meet standards for strength, purity, quality and identity<sup>(٦)</sup>.

This study was undertaken to evaluate the chemical and biopharmaceuticals equivalence of five brands of frusemide tablets in the pharmacies of Mosul city.

## Materials and methods

### Materials

١. The generic products of frusemide used in this study are shown in table ١.

Table ١: Products of frusemide tablets

Name of product	Strength in mg	Manufacturing company	Country of origin	Batch no.
lasimex	٤٠	SDI	Iraq	B ٥
Apix	٤٠	Ajanta	India	AMO١٣٧J
Troge frusemide	٤٠	Troge	Germany	٢٠٣٤-٠١
Desal	٤٠	Biofarma	Turkey	٠٤٠
Salex	٤٠	ADCO	Egypt	٦١٠٢٤٩

٧. Frusemide powder is a gift from SDI Company, Samara-Iraq.

٣. ٠.١ N sodium hydroxide.

٤. Physiological buffer solution Ph ٦.٨.

### Methods

١. **Assay of contents:** Twenty tablets of frusemide were weighed and powdered. ٠.٧g of the powdered frusemide was shaken with ٣٠ ml of ٠.١ N sodium hydroxide for ١٠ minutes; sufficient ٠.١ N sodium hydroxide was then added to produce ٥٠٠ ml. The suspension was then filtered. Five ml of the filtrate was pipetted and diluted to ٢٥٠ ml with ٠.١ N sodium hydroxide. The absorbance of the resulting solution was then measured at the maximum of ٢٧١ nm and the

percentage of contents is calculated from the following formula<sup>٧</sup>.

% content= Absorbance of sample/  
Absorbance of standard × ١٠٠.

٢. **Determination of uniformity of weight:** Twenty tablets from each of the five brands of frusemide were weighed individually using saturius balance. The average weights of the tablets were calculated as well as their percentage of deviation from the average weight<sup>٨</sup>.

٣. **Hardness test.** The crushing strength (hardness) was determined with a tablet hardness tester( Pharma test Company ). Four tablets were randomly selected from each brand and the pressure at which each tablet crushed was recorded<sup>٩</sup>.

4. **Disintegration test.** Six tablets from each brand were employed for the test using disintegration apparatus (Pharma test-Germany) at  $37^{\circ}\text{C}$ . The disintegration time was taken to be the time where no particle remained on the basket of the system<sup>9</sup>.

5. **Dissolution rate determination.** This was determined by using USP dissolution apparatus (paddle). Physiological buffer solution pH 7.4 was used as the dissolution medium and the temperature of the medium was maintained at  $37 \pm 0.5^{\circ}\text{C}$ . One tablet was placed in a basket, which was lowered into the medium and the basket was rotated at 100 r.p.m. Samples (10 ml) were withdrawn at timed interval 0, 10, 20, 30, 40 minutes and replaced with 10 ml fresh dissolution medium after each sampling. The samples were filtered and diluted appropriately before the absorbances were measured at 271 nm using spectrophotometer<sup>9</sup>.

6. **Buffer Preparation.** A pH of 7.4 phosphate buffer was prepared according to USP XII by mixing solution A and B, solution A was prepared by dissolving 14 gm of potassium dihydrogen phosphate in 120 ml of distilled water (DW), while solution B was prepared by dissolving 3 gm of sodium hydroxide in 350 ml of DW and the buffer was prepared by mixing all the amount of solution A with 280 ml of solution B then complete the volume to 200 ml with DW after that the pH is adjusted to 7.4 with solution B.

## Results

1. **Assay of contents.** The content of frusemide in each sample was determined based on the calibration curve generated at 271 nm. The calibration curve was linear and the regression equation for the calibration curve was  $R^2 = 0.9998$  as shown in fig. 1. The percentage of content of each brand is shown in table 2.

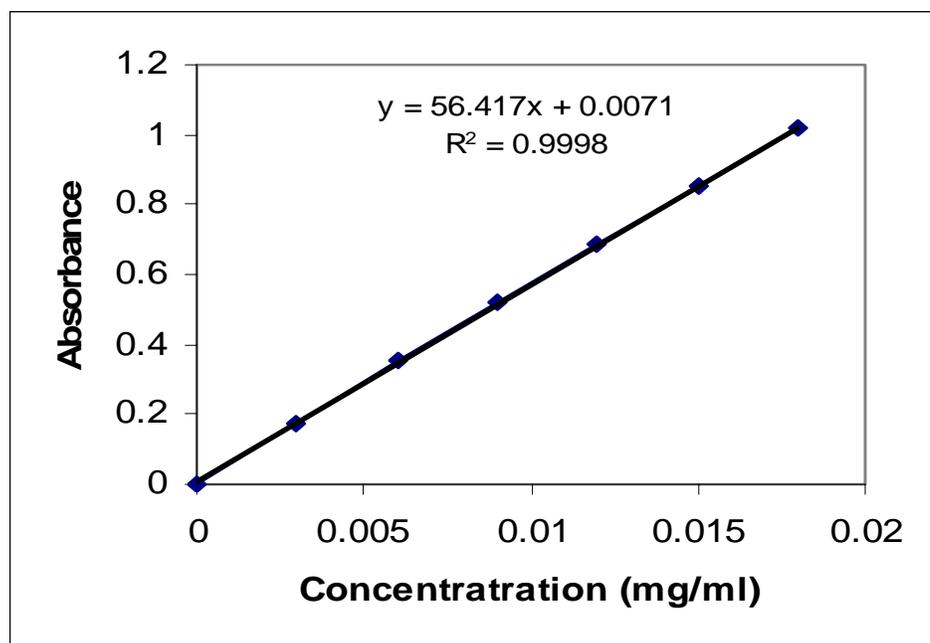


Figure 1: Calibration curve of frusemide

Table ٢. The percent of content of frusemide tablets

Name of product	Percent of content	Actual content in mg
Apix	٩٧.٧٢٧%	٣٩.١
Desal	١٠١.٠٥٥%	٤٠.٤
SDI	١٠١.٦٧%	٤٠.٦٧
Troge	١٠٣.٥٥٥%	٤١.٤
Salex	١٠٥.٢%	٤٢.٧

٣. The summary of the average weight, the percent deviation from average weight, disintegration time, and hardness of the five brands of frusemide tablets is shown in table ٣.

Table ٣. Average weight, % deviation from average weight, disintegration time, and hardness of five brands of frusemide tablets

Brand name	Average weight (g)	% Deviation from average weight	Average disintegration time	Average hardness test Kg/ cm <sup>2</sup>
Apix	٠.٢١	<١	٦.٥ minutes	٧.٩
Desal	٠.١٩٩	<١	٣٧ seconds	٦.٦
SDI	٠.١٥٨	<١	٥٠ seconds	٣.١
Troge	٠.١٧٨	<١	١.٤٦ minutes	٥.١
Salex	٠.١٤٩	<١	٥.١٢ minutes	٣.٧

3. Dissolution rate determination: The dissolution profile of five brand of

frusemide tablets is shown in fig. 3.

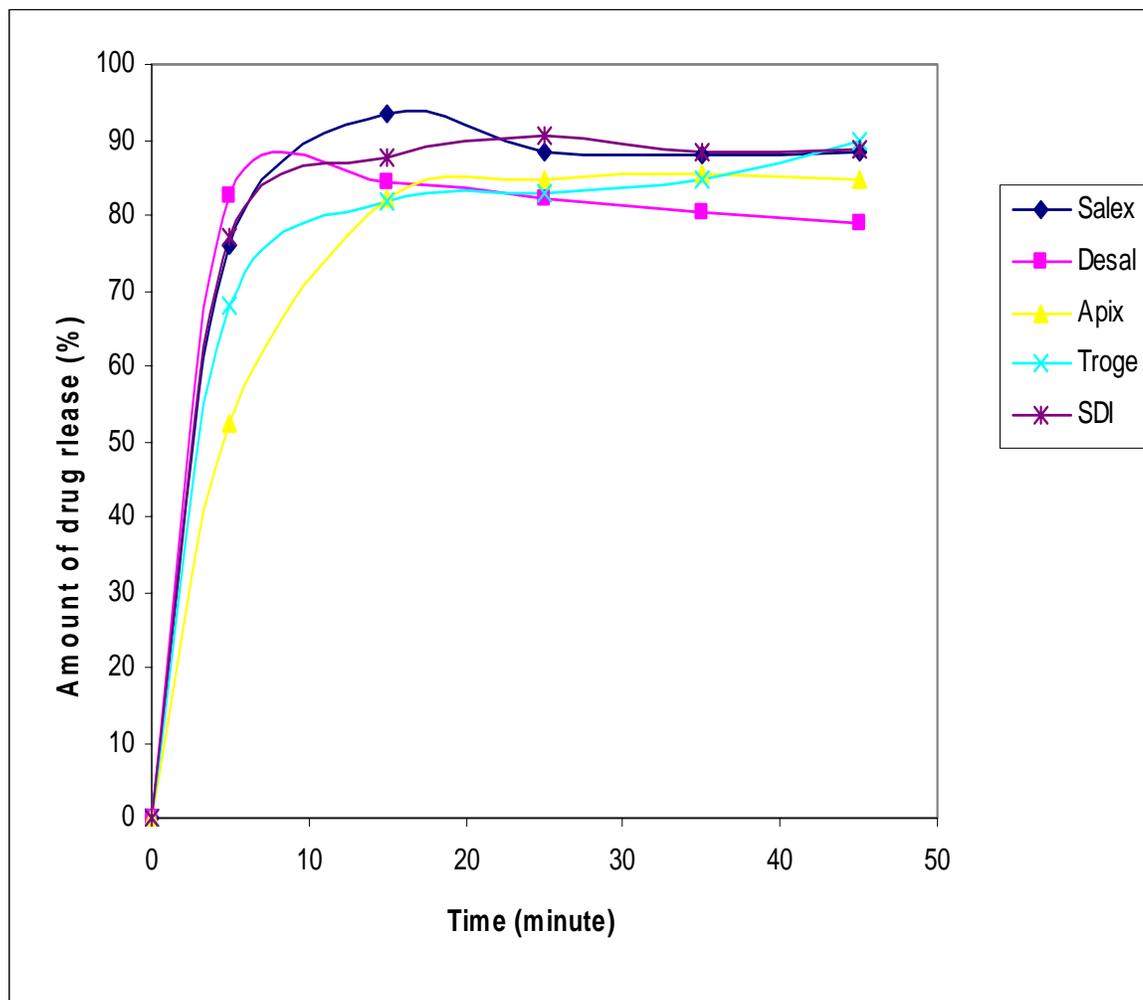


Figure 3. Dissolution profile of five brands of frusemide tablets in phosphate buffer at  $37 \pm 0.5^\circ\text{C}$

**Discussion**

All the brands used were within their shelf life as at the time of the study. Five different brands of frusemide tablets obtained from different manufacturing companies and from different countries were subjected to a number of tests in order to assess their chemical and biopharmaceutical equivalence.

About tablets contents, the highest content was found in Saalex brand (100.2 %) and the lowest one in Apix brand (97.7 %) but still the content of all brands is within

United State Pharmacopeia (USP-29) specifications who stated that "Frusemide tablets contain not less than 90% and not more than 110% percent of the labeled amount frusemide".

Uniformity of weight does serve as a pointer to good manufacturing practices (GMP) as well as amount of the active pharmaceutical ingredient, frusemide contained in the formulation. The average weight of all brands as well as the deviation from the average weight is presented in table 2, it showed that the deviation of all

brands is less than 1% and this complied with the compendial specification for uniformity of weight.

Disintegration could be directly related to dissolution and subsequent bioavailability of a drug. A drug incorporated in a tablet is released rapidly as the tablet disintegrates; a crucial step for immediate release dosage forms because the rate of disintegration affects the dissolution and subsequently the therapeutic efficacy of the medicine.

In this study, the brand Apix gives the slowest disintegration time (7.0 minutes). This high disintegration time of this brand may reflect the high crushing strength (hardness) that this brand give which was 7.9 Kg/cm<sup>2</sup> ( the hardest tablet of all brands) this high disintegration time may affect the dissolution rate of this brand as shown later.

But still the above disintegration time of all the brands is within British Pharmacopeia (BP) and (USP-30) specification. The BP specification is that uncoated tablets should disintegrate within 10 minutes and film coated in 30 minutes while USP specifies that uncoated and film coated tablets should disintegrates within 30 minutes.

Dissolution testing, a surrogate marker for bioequivalence test is indeed a practical and economic approach in developing countries where technology and resources are limited for in vivo studies. One of the values of dissolution test is that it can be used to identify bioavailability problems and assess the need for in vivo bioavailability<sup>11</sup>.

The release of active pharmaceutical ingredient from drug product, the dissolution of the drug under physiological conditions and the permeability across the GIT determines the drug absorption. Based on this, in vitro dissolution may be vital in assessing in vivo performance. Dissolution testing also serves as a tool to distinguish between acceptable and nonacceptable drug products<sup>12</sup>.

In our study, the highest dissolution rate was found in the brand Desal where about 82.04% of the drug is released during the first 0 minutes of the dissolution procedures and this comply with disintegration time obtained for this brand where this brand give the most rapid disintegration time (37 seconds) while the lowest dissolution rate was found in the brand Apix and only about 02.4% of the drug released during the first 0 minutes of the procedure and again, this brand (Apix) give the longest disintegration time (7.0 minutes).

All the brands in this study give dissolution profile within the acceptable range of the USP who stated that "not less than 80% of the labeled amount of frusemide is dissolved in 60 minutes" and all the brands released more than this amount in less than this time.

In conclusion, although this study showed that there are differences between the brands in many of the parameters tested but still these differences are within acceptable ranges according to the USP and BP and these brands may be used interchangeably.

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