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Short communication

A comparative evaluation of furosemide tablets marketed in Libya

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Abstract: Furosemide is a widely potent diuretic drug used in the management of edema and hypertension. Various brands of furosemide are available in the Libyan market and should be subjected to different quality control tests to assess their pharmaceutical equivalence. This study aimed to assess and compare the quality and the pharmaceutical equivalence of some generic brands of furosemide 40 mg tablets marketed in Libya. The pharmaceutical quality of four brands of furosemide tablets was investigated using official and unofficial compendia standards including uniformity of weight, friability, thickness, hardness, drug content and dissolution rate. The results obtained showed acceptable external features as well as the thickness, diameter and uniformity of weight for all the furosemide tablets. The tested brands complied with the official specifications of friability, hardness and drug content. In conclusion, all four brands can be considered as bioequivalence and thus can be pharmaceutically substituted in clinical practice.

Introduction

Most patients with hypertension need drug treatment to reduce their blood pressure. There are different groups of anti-hypertensive drugs used to control blood pressure such as calcium-channel blockers, diuretics, β-blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. Diuretics and calcium channel blockers are two of the most significant groups used for hypertension treatment [1]. Furosemide, 4-Chloro2-[(furan-2-ylmethyl) amino]-5-sulfamoylbenzoic acid ($C_{12}H_{11}Cl\ N_2O_5\ S$), is a potent diuretic drug used in the management of edema, acute and chronic heart failure as well as severe hypertension [2]. It is white, crystalline powder with molecular weight of 330.7 g/mol [3]. Tablets are the most commonly preferable oral dosage forms that contain active ingredients in combination with excipients to provide desired properties that can affect the stability and the effectiveness of the formulation [4]. Tablets are prepared by compressing the powder or granulated mixtures using a tablet machine [5, 6] deliver the correct dose of the drug with the protection of its chemical integrity to the desired location of action [7]. Coated tablets are tablets coated with an inert

substance to protect the drug from dissolution in gastric juice; however, tablets should freely dissolve and liberate the drug in the intestines [5, 6]. After oral administration of the drug, the absorption is sometimes incomplete because of improper dissolution and thus it leads to the insufficient amount of drug reaching the bloodstream [8]. Generic drug products are chemically equivalent to their brand name counterparts in terms of containing the same amount of active ingredients in identical dosage forms, strength, and route of administration, quality, purity, and intended use but may differ in color, shape, excipients, labeling and the expiration date [9-11]. The use of generic medicines has been increasing in recent years as a real competitor for the innovator ones due to their lower costs. [12-14]. However, this could lead to the existence of counterfeit or substandard medicines in higher percentages particularly in developing countries with the lack of supply of essential medicines, unaffordable prices and poor drug quality regulatory systems [11-14]. Although the parent drug is a cutting-edge product that is available to use with advantages of high quality and effectiveness, however, it can be expensive for some patients. For this reason, some patients may prefer taking generic products with lower cost over the high cost of some branded products. Evaluation of the physicochemical characteristics of different brands of pharmaceutical products is very important to assess their bioavailability and pharmaceutical equivalence. When the generic product displays bioequivalence and therapeutic equivalence with the innovator, interchangeability is allowed [15]. The quality of the drugs can be evaluated using *in vivo* or *in vitro* tests [16].

In order to assess the physicochemical properties of pharmaceutical products, various tests are utilized as friability, hardness, weight variation, content of the active ingredient, disintegration and dissolution [17, 18]. The present study was conducted to evaluate and assess the quality of four furosemide tablet brands available in the Libyan market and to ascertain that all the tested brands are pharmaceutically equivalent.

Materials and methods

Furosemide tablets with a label strength of 40 mg were purchased from local pharmacy stores in Tripoli City, Libya. All the tests were performed within product expiration dates. The furosemide powder standard (99.6%) was obtained from Sigma Aldrich Co. LLC., USA. All the reagents and solvents used were of pharmaceutical grade. Study samples were coded as shown in **Table 1**

Table 1: Commercial furosemide tablets available in the Libyan market

Brand	Name	Manufacturer
A	Furo-Denk	XXXX
B	Lasix	XXXX
C	Lasilix	XXXX
D	Furosemide	XXXX

The following instruments were used for the *in vitro* quality control assessment of furosemide tablets. Assay by UV-spectroscopy, analytic Jena-spaced, 200, model, Germany, tablet combination tester for hardness, diameter and thickness, friability tester, disintegration time tester apparatus, dissolution tester DT50. Visual inspection: The diameter and thickness of the four tablets from each brand were measured and the average value and standard deviation were calculated.

Weight variation: Twenty tablets from each brand were randomly selected and their weights were measured. Then the average weight of each brand was calculated and the percentage deviation of each tablet weight from the average weight and the standard deviation were determined.

Hardness test: The hardness, thickness, and diameter of the tablets were determined using a tablet combination tester. In the hardness test, twenty tablets were randomly selected from each brand and the pressure was applied and the force required to break up the tablet was recorded in newtons (N). The average force and the standard deviation of each sample were calculated [3]. Tablet thickness and diameter should be controlled within ± 5.0% of a standard value [19, 20].

Friability test: Twenty tablets were randomly taken from each brand and the loose dust was removed then the tablets were accurately weighed and placed in the friabilator. The samples were allowed to rotate with a total of 100 revolutions (25 rpm/min) then they were removed, de-dusted and reweighed and the percentage of friability for each brand was calculated using the following formula

$$\textbf{Friability (\%)} = \frac{\textbf{initial weight - final weight}}{\textbf{initial weight}} \times \textbf{100}$$

Dissolution test: The *in vitro* release of the drug was investigated by USP dissolution test apparatus II, using a dissolution tester. The test was performed in 900 ml of phosphate buffer pH 5.8 maintained at 37±0.5 °C and the apparatus was operated at 50 rpm. Samples were withdrawn at intervals of 15, 30, 45, and 60 min, filtered, diluted and the absorbance was measured at 277 nm using pure medium as a blank. The percentage of average drug release for each brand was plotted against time.

Assay of furosemide tablets: Twenty tablets were weighed and powdered. A quantity of the powder containing 0.2 g of furosemide was mixed with 300 ml of 0.1 M sodium hydroxide for 10 min. A sufficient amount of 0.1M sodium hydroxide solution was added to produce 500 ml and the solution was filtered. 5 ml of the filtrate was diluted to 250 ml with 0.1 M sodium hydroxide solution and the absorbance of the resulting solution was measured at the maximum at 271 nm using a UV-VIS spectrophotometer and the percent content was determined.

Results and discussion

Four commercial brands of furosemide tablets were assessed to evaluate their pharmaceutical quality to reduce the existence of poor-quality drugs in the market. All the brands were subjected to various official tests to assess their dissolution and other valuable parameters such as weight variation, hardness, friability and the drug content assay.

Weight variation: This test is used to confirm that each batch contains tablets of appropriate size and their contents are within the accepted range. All the brands of furosemide tablets were consistent in their weight and showed uniform geometrical dimension parameters (**Table 2 and Figure 1**). Tablets of the same formulation should have the same appearance in terms of color, shape and size. The deviation of tablet weight from the average weight was within the acceptable limit that none of the tablet weight were deviated from the average weight by ±7.5%. The difference in the average weights could be a result of using various excipients with different characteristics and properties during their preparations. All the brands revealed similar thickness (2.2-3.3 mm) and diameter of about 8 mm except sample A its diameter was 5.98 mm. Both the thickness and diameter of the tablets are important factors for patient compliance and drug efficacy. Ensuring the consistency of tablet thickness during batches of the same formulations can be accomplished by using the same compression force for the same amount of the drug-filled in the machine. The same dosage forms of different manufacturer origin should not be expected to have the same properties and efficacy and as a result, evaluation of these brands to investigate their characteristics and their bioavailability is important to ensure their bioequivalence [21-23].

Hardness test: The tablets should be of a suitable mechanical strength to tolerate any erosion or chipping that can happen during handling, manufacturing and transportation [24]. The results showed that the hardness of all the tested samples was in the range of 67.6-100.3 N (**Table 2**). A force of 40 N is the minimum requirement to achieve an acceptable hardness of the tablets. Accordingly, all the tested tablets had satisfactory hardness. Brand C showed to have the highest hardness while brand D had the lowest value of hardness which indicated that brand C required the highest pressure load to cause tablet to break up compared to other samples. Brand C has been shown to have the lowest percentage of weight loss and the highest hardness compared to other tested brands. Hardness is an important tool that can affect the disintegration and dissolution rate

of the tablet [24]. Hardness has a direct relation with the friability and disintegration of the tablets. Manufacturing of harder tablets will lead to an inadequate dissolution rate with an increase in their disintegration time [25-27]. In contrast, less hard tablet is expected to be more friable and take less time to disintegrate which in turn will affect the drug's bioavailability [28]. Thus, it is of important requirement to assess the tablet hardness as it can lead to possible bioavailability issues or a change in the dissolution rate of the drug.

Friability test: The percentage friability of the tested samples was in the range of (0.1-0.4%) as shown in **Table 2** which inferred that all the tablets were within the limit percentage friability should be less than 1.0% according to USP specification [29]. Accordingly, all the tablets had good strength that could resist any chipping or shock during their handling and transportation. The percentage of friability decreases as the hardness of the tablet increases and vice versa. The high friability is an indication to the chipping or erosion of the tablet that may cause the loss of the active ingredient and thus could lead to weight variation or content uniformity problems [30, 31].

To ensure complete absorption of the orally administered drugs in tablet dosage form, they have to be completely dissolved in gastrointestinal fluid before their absorption [32]. *In vitro* dissolution test measures the time required for the tablet to release the specified percentage of a drug into a solution under specified conditions and this parameter can be used to provide information about drug absorption and bioavailability [33, 34]. The dissolution profiles of four investigated generic drugs (released drugs) were within the limit range (**Figure 2**) since the drug release values were more than 80% in 60 minutes (**Figure 3**).

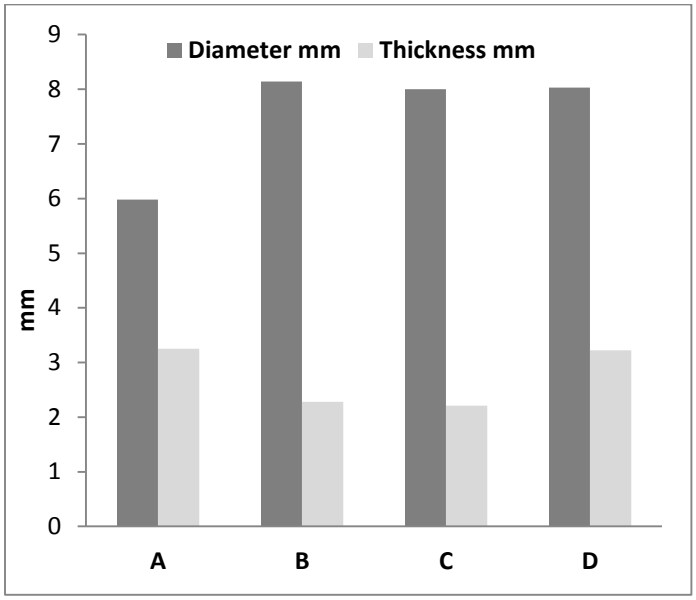

Figure 1: Thickness and diameter (mm) of the furosemide tablet brands

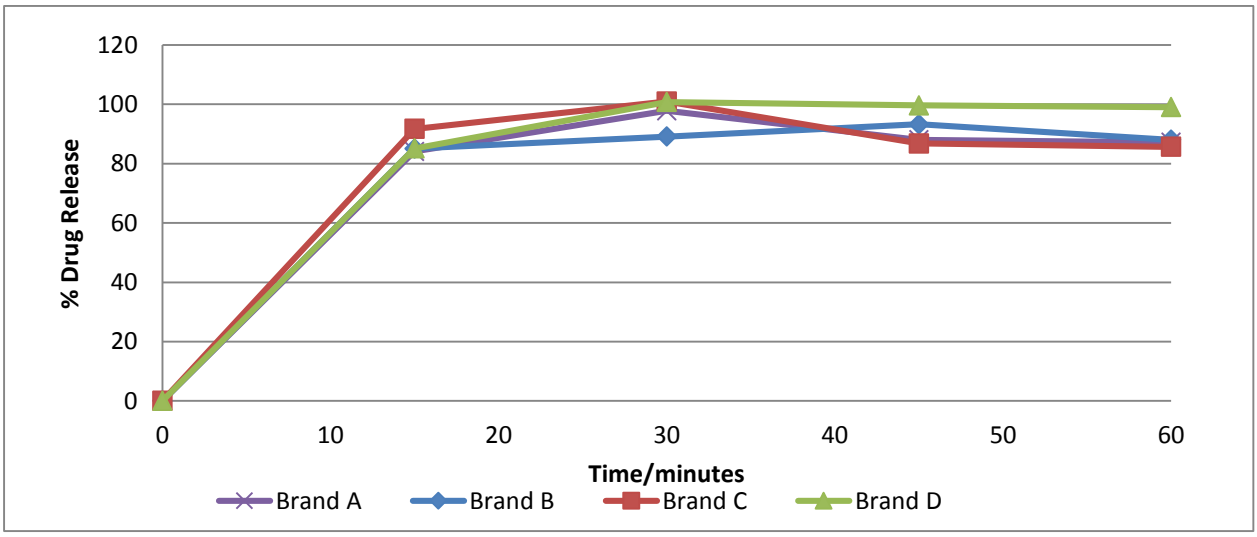

Figure 1: Dissolution profile of different brands of furosemide tablet

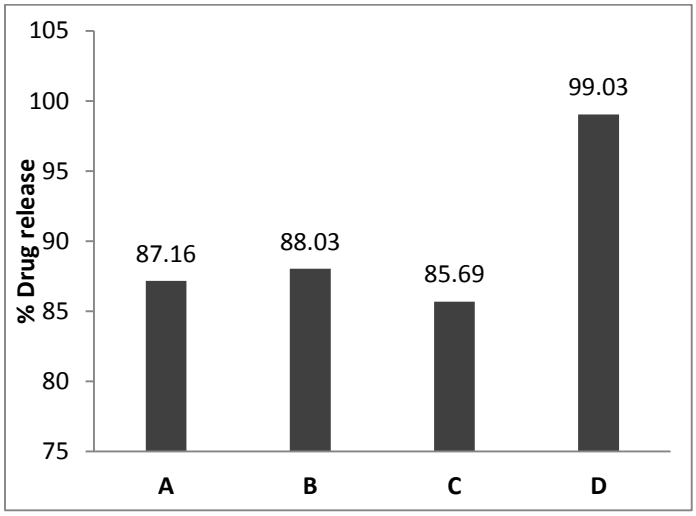

Figure 2: Dissolution rate profiles for furosemide tablet brands at 60 minute

Content of active ingredient (assay): The content of furosemide was determined in all the tested brands and ranged from 95.0% (D) to 99.1% (A) as shown in **Table 2 and Figure 4** which were within the specified limit (95-105%). Assay of pharmaceutical products is a critical test to ensure that the dosage form contains the labeled amount of drug where the pharmaceutical products are considered of poor quality if they fail to contain the right amount of the active ingredient [35, 36]. An inadequate amount of the drug can lead to under dosing and incorrect treatment whereas higher amount of active ingredients can lead to poor therapeutic outcomes with an increased risk of adverse drug reactions and toxicity.

Table 2: Physicochemical properties of different brands of furosemide tablet

Brand	Average weight (mg)	% Weight variation	Diameter (mm)	Thickness (mm)	Hardness (N)	Friability (%)	Assay in %
A	100.87	±1.88	5.98	3.25	70.3	0.38	99.1
B	162.49	±1.57	8.14	2.28	74.8	0.33	99.03
C	156.92	±2.18	8.00	2.21	100.3	0.11	95.1
D	217.51	±1.58	8.03	3.22	67.6	0.44	95

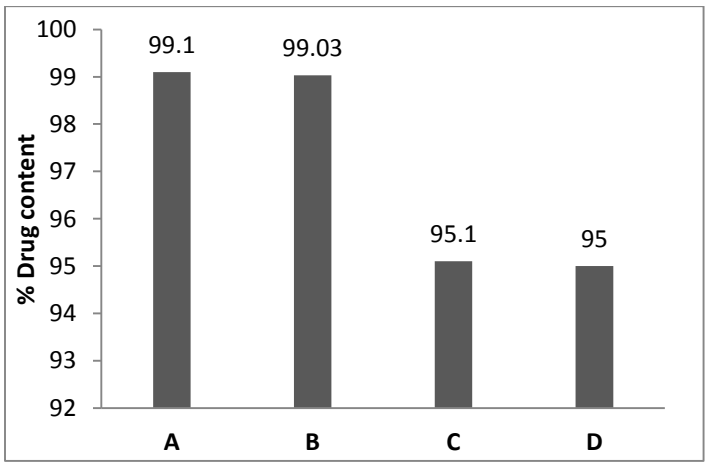

Figure 4: Content of furosemide brands in percentage

Conclusion: The generic brands of furosemide tablets available in the Libyan market complied with pharmacopoeia standards in which there was no significant variation in the quality of those tested brands. Therefore, it can be concluded that furosemide brands are pharmaceutically equivalent and can be interchangeable in clinical practice. This study highlights the importance of strict monitoring of pharmaceutical products in the markets especially in developing countries to ensure the quality and therapeutic equivalence of the products.

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Ethical issues: Including plagiarism, informed consent, data fabrication or falsification, and double publication or submission have completely been observed by authors.
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References

1. Cooper-DeHoff RM, Pepine CJ (2010) The use of diuretics plus calcium channel blockers for hypertension may be associated with a higher risk of myocardial infarction but not stroke compared with the combination of diuretics plus β blockers. Evidence Based Medicine. 15 (3): 92-93. doi: 10.1136/ebm1067
2. Katzung BG (2012) Basic and clinical pharmacology. 14th ed. Mc Graw Hill. ISBN: 978-1259641152.
3. British Pharmacopeia (2009) The stationery office/TSO, London. 1st ed., vol. 1-4. ISBN: 9780113227990.
4. Aulton ME (2007) The design and manufacture of medicines, third edition. Elsevier limited, UK. ISBN: 9780443101083.
5. Ansel HC (1981) Introduction to pharmaceutical dosage forms. 3rd ed., Lea & Febiger, Philadelphia, USA. ISBN: 0812107713.
6. Perumalla SR, Sun CC (2014) Enabling tablet product development of 5-fluorocytosine through integrated crystal and particle engineering. Journal of Pharmaceutical Sciences. 103 (4): 1126-1132. doi: 10.1002/jps.23876
7. Kumare MM, Marathe RP, Kawade RM, Ghante MH, Shendarkar GR (2013) Design of fast dissolving tablet of atenolol using novel co processed superdisintegrant. Asian Journal of Pharmaceutical and Clinical Research. 6 (3): 81-85. Corpus ID: 11257135.
8. Banker GS, Rhodes CT (2002) Modern pharmaceutics. 4th ed. Marcel Dekker Inc, New York. ISBN: 9780824706746.
9. Kesselheim AS, Misono AS, Lee JL (2008) Clinical equivalence of generic and brand-name drugs used in cardiovascular diseases: a systemic review and meta-analysis. JAMA. 300: 2514-2526. doi: 10.1001/jama. 2008.758
10. Strom BL (1987) Generic drug substitution revisited. The New England Journal of Medicine. 316 (23): 1456-1462. doi: 10.1056/NEJM198706043162306
11. Food and Drug Administration (2004) Center for Drug Evaluation and Research (CDER). http//www.fda. gov/cder /reports/rtn/2004/rtn2004. (Accessed on 1/6/2023).
12. Gackson G, Arver S, Banks I, Stecher J (2010) Review article: counterfeit phosphodiesterase type 5 inhibitors pose significant safety risks. International Journal of Clinical Practice. 64 (4): 497-504. doi: 10.1111/j.1742-1241. 2009.02328.x
13. Khuluza F (2014) In vitro evaluation of the quality of paracetamol and cotrimoxazole tablets used in Malawi based on pharmacopeial standards. Malawi Medical Journal. 26 (2): 38-41. PMID: 25157315; PMCID: PMC4141240.
14. Olayemi SO, Akinleye MO, Awodele EO, Idris O, Oladimeji-Salami J (2012) The physicochemical equivalence of eight brands of amlodipine in Logos, Nigeria. West Africain Journal of Medicine. 31 (3): 154-159. PMID: 23310934.
15. Nguyen TA, Knight R, Roughead EE, Brooks G, Mant A (2015) Policy options for pharmaceutical pricing and purchasing: issues for low- and middle-income countries. Health Policy and Planning. 30 (2): 267-280. doi: 10.1093/heapol/czt105
16. Abebe S, Ketema G, Kassahun H (2020) In vitro comparative quality assessment of different brands of furosemide tablets marketed in Northwest Ethiopia. Drug Design Development and Therapy. 14: 5119-5128. doi: 10.2147/ DDDT.S280203
17. Abozaid DM, Saleh WM (2022) Evaluation of some metformin hydrochloride brands available in Libyan market. Mediterranean Journal of Pharmacy and Pharmaceutical Sciences. 2 (4): 6-12. doi: 10.5281/zenodo.7479690

18. Afifi SA, Ahmadeen S (2012) A comparative study for evaluation of different brands of metformin hydrochloride 500 mg tablets marketed in Saudi Arabia. Life Science Journal. 9 (4): 4260-4266. doi: 10.7537/marslsj090412.636
19. Gennaro AR (1995) Remington: the science and practice of pharmacy. 19th edition, Williams & Wilkins Publishing, Easton. ISBN: 978-0912734040.
20. British Pharmacopoeia (2002) Appendix: XII. Stationery Office, UK. ISBN: 9780113225750.
21. Khan LG, Razvi N, Anjum F, Siddiqui SA, Ghayas S (2014) Effects of various excipients on tizanidine hydrochloride tablets prepared by direct compression. Pakistan Journal of Pharmaceutical Sciences. 27 (5): 1249-1254. PMID: 25176379.
22. Khan MQ, Razvi N, Anjum F, Ghazal L, Siddiqui SA, Ghayas S (2014) Evaluation and comparison of different brands of domperidone tablets available in Karachi, Pakistan. Pakistan Journal of Pharmaceutical Sciences. 27 (4): 935-938. PMID: 25015463.
23. Muselik J, Franc A, Dolezel P, Goněc R, Krondiová A, Lukášová I (2014) Influence of process parameters on content uniformity of a low dose active pharmaceutical ingredient in a tablet formulation according to GMP. Acta Pharmaceutica. 64 (3): 355-367. doi: 10.2478/acph-2014-0022
24. Troy DB (2006) Remington: the science and practice of pharmacy. 21st ed. Philadelphia, PA: Lippincott, Williams & Wilkins. ISBN: 9780781746731.
25. Yau MK, Meyer MC (1981) In-vivo in-vitro correlation with a commercial dissolution simulator 1, methenamine, nitrofurantion and chlorothiazide. Journal of Pharmaceutical Sciences. 70 (9): 1017-1024. doi: 10.1002/jps. 2600700913
26. Hambisa S, belew S, Suleman S (2019) In vitro comparative quality assessment of different brands of norfloxacin tablets available in Jimma, Southwest Ethiopia. Drug Design, Development and Therapy. 13: 1241-1249. doi: 10.2147/DDDT.S189524
27. Morshed N (2015) Comparative evaluation of prednisolone 5mg tablets marketed in Bangladesh. World Journal of Pharmaceutical Research. 4 (5): 277-289. Corpus ID: 73747781.
28. Baig A, Quraishi AR, Zahir F (2013) Post-market in-vitro comparative evaluation of quality control parameters of paracetamol compressed tablets manufactured in local industrial zones of Kpk Pakistan. The Pharma Innovation Journal. 2 (3, Part A): 11-15. doi: Nil.
29. The United States Pharmacopeia (2015) The United States pharmacopeia: The national formulary. ISBN: 9781936424443.
30. Tuli BM (2014) Evaluation of pharmaceutical equivalence of two different brands (Limaryl and Dactus) of Glimepiride tablets (2mg) available in Bangladesh. Department of Pharmacy, East West University. Aftabnagar, Dhaka, Bangladesh. Thesis. Corpus ID: 111263809.
31. Allen L, Ansel HC (2013) Ansel's pharmaceutical dosage forms and drug delivery systems. 10th ed. Wolters Kluwer Health. ISBN: 978-1451188769.
32. Melia CD, Davis SS (1989) Review article: mechanisms of drug release from tablets and capsules. 2: Dissolution. Alimentary Pharmacology and Therapeutics. 3 (6): 513-25. doi: 10.1111/j.1365-2036.1989.tb00243.x
33. Hammarlund MM, Paalzow LK, Odlind B (1984) Pharmacokinetics of furosemide in man after intravenous and oral administration. Application of moment analysis. European Journal of Clinical Pharmacology. 26: 197-207. doi: 10.1007/BF00630286
34. Patel RC, Keraliya RA, Patel MM, Patel NM (2010) Formulation of furosemide solid dispersion with micro-crystalline cellulose for achieve rapid dissolution. Journal of Advanced Pharmaceutical Technology and Research. 1 (2): 180-189. PMID: 22247844; PMCID: PMC3255424.
35. Gupta MM (2019) quality control testing of different brands of conventional tablets of ibuprofen available in Trinidad & Tobago, West Indies: an in-vitro testing. Faculty of Medical Sciences, Research Day; March 2019. ID: biblio-1025491.
36. Almdaaf MA, Altriki MS, Elnekaib MA (2023) Post-marketing quality assessment of paracetamol brands in the Libyan market. Mediterranean Journal of Pharmacy and Pharmaceutical Sciences. 3 (4): 73-79. doi: 10.5281/ zenodo.10289340