Research Article

Evaluation of the Pharmaceutical Quality of Some Furosemide Tablet Brands

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ABSTRACT

Furosemide is a widely prescribed and powerful diuretic drug used in the management of edema and hypertension. The market is occupied with different formulations of furosemide for oral use. The aim of this study was to find out the pharmaceutical quality and equivalency of some generic brands of furosemide 40 mg conventional tablets that are dispensed and used in Libya. Five commercial brands of furosemide tablets were selected and their physicochemical properties were investigated according to the official compendia standards. The samples were inspected for their color and appearance. The evaluation process also involved conducting of weight variation, hardness, friability, disintegration time, assay of drug content, dissolution rate, and microbial contamination tests. Results obtained revealed that all the brands showed acceptable external features and exhibited uniformity in diameter, thickness and weight. All the brands demonstrated sufficient mechanical strength to resist fracture and crumbling. Additionally, samples were in compliance with the specifications of drug content and disintegration time. The *in vitro* release performance of the brands efficiently complied with the official limits. All the brands demonstrated optimum physicochemical properties and were in agreement with the microbial specifications. Therefore, it can be expected for the investigated brands to show equivalent therapeutic effect and can be potentially interchangeable.

Keywords: Furosemide; Tablet dosage form; Physicochemical properties.

INTRODUCTION

Tablets for oral drug administration are the most commonly preferred and used dosage form. Tablets are solid unit dosage form containing a blend of active medical substance(s) in combination with suitable pharmaceutical excipients which are added to provide desired properties that influence their effectiveness and stability.[1] Tablets are usually manufactured by compression using tablet machines that exert pressure to compact powdered or granulated mixtures, tablets may also prepared by molding.[2,3] The popularity of tablets is attributed to their accurate dosing of drugs, physical and chemical stability, convenience in handling and use, low cost, and ease of manufacture.[4,5] Tablets are subjected to several tests that are designed and developed to assure their therapeutic efficacy and safety. Quality control tests are performed on samples of tablets that are withdrawn periodically during tablet manufacture and on the final product batches. Generic drug products are chemically equivalent to their brand-name counterparts in terms of active ingredients but may differ in other aspects such as color, shape, excipients employed, and manufacturing process.[6,7] The market is full of generic drug products, which represent a real competitor for the innovator ones due to their lower costs. However, this could lead to the existence of substandard medicines and counterfeits, particularly, in areas which have poor drug quality regulatory systems.[8-12]

Furosemide, 5-(aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)amino]-benzoic acid ($C_{12}H_{11}ClN_2O_5S$), is a potent loop diuretic drug used in the treatment of edema of pulmonary, cardiac, hepatic, or renal origin and in the management of chronic hypertension. It is practically insoluble in water and is a weak acidic drug, absorbed mostly in the stomach and upper part of the small intestine.

Formulation of such drugs for efficient oral delivery represents a great challenge to researchers in the pharmaceutical industry. However, advancement in formulation design and development lead to the use of successful strategies and the employment of proper additives to enhance drug release and improve oral bioavailability.[13,14] Many brands of furosemide tablets of different formulation bases and manufacture origin are present in the market. The goal of the present study was to assess and compare the physicochemical quality of several brands of furosemide compressed tablets that are sold in Libya. A real concern about drugs quality has been found because of the appearance of counterfeits in the developing countries.[15] Drugs should be routinely and regularly checked to ascertain that their quality meet the standards and to identify counterfeits.

MATERIALS

Samples of five commercial brands of furosemide 40 mg tablets were collected from the local market (Table 1). The following reagents, hydrochloric acid, sodium hydroxide, monobasic potassium phosphate (KH_2PO_4), tetrahydrofuran THF, Furosemide standard RTC-PHR1057-1G were obtained from Sigma-Aldrich Co. LLC., USA. Acetonitrile HPLC grade (Carlo Erba Reagents, Italy), acetic acid, glacial (Fisher-Scientific, USA) were used in the study. Plate count agar (Difco™), Tryptic soy broth (Bacto™), and Eosin methylene blue agar modified were form (Becton, Dickinson and Co., Sparks, USA & Le pont de claix, France). Sabouraud chloramphinicol agar (Himedia Laboratories, India), Macconkey broth (Oxoid Ltd., Basingstoke, Hampshire, UK). Diluting solution was made by diluting (glacial acetic acid 2.2 % v/v in a mixture of acetonitrile: water 50:50). Media were prepared according to the instructions using heating plate (VELP Scientifica, Italy) and sterilized in an autoclave GFL, Germany.

METHODS

Tablets Appearance

Samples of 20 tablets from each batch were randomly selected and visually inspected for their external characters such as color, shape, surface texture and shape, presence of grooves, monograms and surface defects.

Weight Variation

Samples of twenty tablets from each brand were randomly selected, their individual weights were measured and recorded. The average weight of each sample was calculated and the deviation of each tablet weight from the average weight was determined. The batch is considered to comply with the USP specifications if the weights of not more than 2 of the tablets differ from average weight by no more than the percentage permitted (±7.5%) and no tablet differs by more than double that percentage (±15%).

Hardness and Geometrical Parameters

The hardness, thickness, and diameter of samples of 10 tablets were determined using tablet combination tester (Erweka TBH 320 WTD Multi-Check tester, Germany). In the hardness test, pressure was applied on the tablet and the force caused the tablet to break up was recorded. The optimum hardness regarded for uncoated tablet is 4-8 kg/cm^2. Tablet thickness and diameter should be controlled within a ±5% of a standard value.

Friability

Samples of 20 tablets from each batch were randomly selected and weighed. Tablets were placed in the plastic chamber of the friabilator TDR with balance (Erweka, Germany) and allowed to rotate and drop a distance of 6 inches at each revolution for 100 revolutions (25 rpm/minute). The tablets were removed, de-dusted, reweighed and the percentage friability was calculated using the following equation:

$$\%F = \frac{WI \quad WF}{WI}$$

Where, *WI*=Initial weight of tablets,
WF=tablets weight after friability test.

Disintegration Time

Samples of six tablets were selected from the different brands. Tablets were placed in the six tubes of the basket-rack assembly of the disintegration time tester ZT321 (Erweka, Germany). The assembly was allowed to move up and down in 1 liter beaker containing an immersion fluid (maintained at 37±2°C) at 28-32 cycles/minute. The disintegration time was recorded at the moment where no particles remained on the mesh of the basket-assembly.

Assay of Drug Content

High-performance liquid chromatography (HPLC) assay method (USP29) was used to determine the active drug content in the furosemide tablet brands. The system Prominence UFLC (Shimadzu, North America) included, LC-20AD pump, SIL-20A$_{MT}$ autosampler, Waters XSelect-ODS reverse-phase C18 column I00Å, 250 mm x 4.6 mm i.d., 5-µm particle size L1 (Waters corporation,

USA), CTO-20AC column oven, SPD-20 AV UV/Vis detector, and CBM-20A communications bus modules HPLC system controller. The conditions of the chromatographic analysis are summarized in table 2. The standard and system suitability solutions were prepared according to the procedures in USP29 using diluting solution. Samples solutions were made by transferring an accurately weighed amount (Shimadzu AUW220D-balance) from the powdered tablets equivalent to 50 mg of furosemide to a-50 mL volumetric flask, diluting solution was added to volume, shacked for 15 minutes (Flask shaker SF1, Stuart Scientific, UK).

Dissolution Rate Test

The *in vitro* release rate of the drug was studied using USP dissolution test apparatus II, using dissolution tester DT600 (Erweka, Germany). The dissolution was performed in 900 ml of phosphate buffer pH 5.8 maintained at 37±0.5°C, the paddles were rotated at 50 rpm and 5mL samples were withdrawn. The collected dissolution samples were filtered through a Whatmann filter paper, diluted when required and the amount of drug dissolved was determined using HPLC-UV/Vis at 254nm. Drug dissolution is expressed as the percent of drug content occurring after a given time interval under specified conditions. As its specified in the USP, not less than 80% (Q) of the labeled quantity of the drug is dissolved in 60 minutes.

Total Aerobic Microbial Count TAMC (Pour-plate method)

Test for quantitative enumeration of mesophilic bacteria and fungi that may grow under aerobic conditions. Samples were randomly selected, prepared and appropriately diluted according to the described procedures in the section preparation of the sample in EP and USP. 1 ml from the diluted samples was transferred to two sterile Petri dishes and 15-20 ml of Soybean-Casein Digest Agar Medium (45°C) was promptly added to each dish. The Petri dishes were covered, gently mixed by simple rotation/tilting and allowed to cool at room temperature to solidify the contents. The dishes were incubated for 3-5 days at 30-35°C (Incubator IN30 Memmert, Germany). At the end of incubation time, the plates were examined for the growth of microbial colonies. The arithmetic mean per culture medium of the counts for each two plates were taken and the number of colony-forming units per gram of product was calculated. If there is no colonies, the result is expressed as less than 10 microorganisms per g of specimen. Similarly, samples were proceeded for total combined molds and yeast count, except the medium used was Sabouraud Dextrose Agar Medium. Samples were incubated for 5 to 7 days at 20° to 25°C.

Escherichia Coli

I mL (≥ 1 g) of the diluted samples were used to inoculate Casein soyabean digest broth, mixed and incubated at 30-35°C for 18-24 hours. The containers were shacked,1 mL of the broth was transferred to 100 mL of MacConkey broth and incubated at 42-44°C for 24-48 hours, subcultured on plates of MacConkey agar at 30-35°C for 18-72 hours. Growth of colonies indicates the possible presence of E. coli and this can be further confirmed by identification tests using Eosin-Methylene Blue Agar medium. The product is complies with the test if no colonies are present or if the identification tests are negative.

RESULTS AND DISCUSSION

Five commercial generic brands of furosemide 40mg conventional tablets (Table 1) were assessed for their pharmaceutical quality according to the described requirements in the official compendia. The evaluation tests were performed on the samples while in their intended shelf life. In general, tablets should be elegant in their appearance to be accepted by the patient. As described in table 3, brands B, C, D and E were flat disc-shaped tablets with slightly beveled edges and white in color. While brand A was round curved-faced tablets and yellowish-white in color. All tablets were with smooth and intact surfaces and displayed homogenous color appearance. Presence of any surface defects or color changes in tablets would provide an indication of problems related to the manufacturing procedures or physical or chemical stability.[16,17]

Surface shape of tablets is determined by the punches, using punches with flat faces produce flat tablets, while concave punches produce tablets with different levels of convexity. Brand A was marked with two crossed break lines, which could facilitate their double break down into quarters (Table 3). All other brands were scored in halves, which could facilitate their accurate breaking in to equal parts. Presence of score lines on tablets allow the ease of tablet splitting for dose flexibility, reducing the cost of prescriptions, and administration of smaller parts of tablet for patients have difficulty in swallowing. Therefore, patients can adjust the dose in response to medication effects or to comply with the labeled dosage and

administration instructions.[18] However, variations in drug dose can be happen with manual subdivision of tablets in case if the dose is less than one tablet.[19] Therefore, high caution should be taken in the division of furosemide tablets to avoid low therapeutic efficacy or unwanted side effects. As summarized in table 3, brands B, C, D, and E were engraved with symbols indicating the drug name, its strength and the company name or logo for further products identification. All brands of furosemide tablets were consistent in their weight and exhibited uniform geometrical dimension parameters (Table 4 and Figure 1). Tablets of the same formulation should be consistent in their appearance, size and weight.

The deviation of the tablets weight from the average weight were in the permitted limit (none of the tablets were deviated from the mean by up to ±7.5%). All brands showed different average weight, different formulations were based on the incorporation of different excipients that have different characteristics and functionality. All the investigated brands exhibited similar diameters (2.3-3.3 mm) and thickness (7.6-8.2 mm). The uniformity in tablets thickness and diameter is essential for patient acceptance, comfort, and packaging efficiency. The uniformity in tablets thickness during batch production and between batches of the same formulation can be achieved by the precise control of the same volume of the fill and the same compression force. It cannot be assumed that the same dosage forms produced by different manufacturers will necessarily demonstrate the same characters and effects. The brands evaluated were of different formulation principles, different excipients, and manufacturing processes, which would have a direct impact on their physicochemical characteristics and pharmaceutical equivalence.[20-25]

The tablet should be of a suitable mechanical strength to withstand fracture and resist chipping and erosion during all types of post manufacture handling. All brands demonstrated ability to withstand pressure during handling, packaging and transportation (2.5-10.6 Kg/cm^2, Table 4). Brand A of the furosemide tablets showed the lowest hardness while brand E had the highest value and required the highest pressure load to break up. All the investigated brands demonstrated acceptable friability and tablet cohesion (less than 1%w/w, Table 4). Brand E demonstrated the lowest percentage loss in weight and the highest hardness compared to the others. Using high levels of compression force during production of tablets will result in harder tablets that do not disintegrate in an appropriate time. Additionally, granulation characteristics have a direct impact on tablets hardness.[26,27] Optimization of formulation design and manufacture procedures and parameters will result in making tablets with adequate characteristics and strength.

Tablets should contain the correct dose of drug for effective therapeutic action and reduced toxicity. The results obtained from the evaluation of active ingredient content were within the limits (95-105%), result is illustrated in figure 2. All brands contained the required amount of drug that complied with the standards. The drug should be released from the tablet in a controlled and reproducible manner. Tablets disintegration is required for their dissolution and the subsequent drug absorption.[28] All brands passed the disintegration time test, tablets were broken up and deaggregated in to their original granules and particles within 15 minutes. Differences in the disintegration time were observed between the generic furosemide 40 mg tablets. Brands B, C, and D were demonstrated very rapid disintegration time compared to the other brands (Table 4). While brand E showed a more prolonged disintegration time (8 minutes). *In vitro* tablet disintegration and dissolution assist in the prediction of drug behavior after being ingested, however, an *in vitro/in vivo* performance correlation have not been clearly established.[29] Tablet is broken down in to granules or particles having higher surface area which facilitate their wetability and dissolution. Tablet's disintegration is affected by the type of disintegrating agent(s) used in the formulation, mechanism of disintegration, disintegrant concentration and the way of its incorporation. It is also influenced by the type and concentration of binder system and the amount of compression force used in the production of tablets.[30-32] It is an essential requirement for drugs administered orally in tablet dosage form to be dissolved by the gastrointestinal fluids at the absorption site before being completely absorbed.[33] Therefore, the dissolution process is a rate-limiting step in drug absorption and bioavailability of poorly soluble drugs and poorly formulated products.[34,35] It is demonstrated that, the solubility of furosemide is the rate-determining step in its gastric absorption. The dissolution rate profiles of the investigated brands were within the standard limit (Figure 3). The drug release values were more than 90% in one hour. It is demonstrated that using different excipients and manufacturing processes can influence drug release kinetics and levels.[36-39] However,

all the assessed brands exhibited similar patterns of drug dissolution.[40] All samples passed the microbial contamination tests, data presented in table 5. This indicated that there was no kind of contamination with pathogenic bacteria or other microbial types.

CONCLUSION

The five generic brands of furosemide 40 mg tablets fulfilled all the pharmacopoeia specifications for weight uniformity, hardness, friability, disintegration time, dissolution, correct dose content, and presence of microbial contaminants. It can be confirmed from the evaluation process that all the brands proved to have similar capability for efficient pharmaceutical and therapeutic performance. In addition, five brands of different formulation design and different manufacturers can be considered equivalent in their physicochemical properties and can be used to substitute each other safely and efficiently. Furthermore, continuous monitoring and control of drug products in the market would prevent the prevalence of counterfeits and sub-standard medicines and ensure the use of medicines of standard quality.

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Table 1: The commercial generic brands of furosemide 40 mg compressed tablets used in the study

Brand	Brand Name	Batch No.	Manufacture Date	Expiry Date	Manufacturer
A	Duresan® 40mg	3501	01/2012	01/2017	PHARMA 5 Pharmaceutical Laboratories, Morocco
B	Furosemide 40mg	AUC112002	05/2012	06/2015	Bristol Laboratories Ltd., UK
C	Furosemide 40mg	LK10920	07/2010	06/2013	CP Pharmaceuticals Ltd., Wrexham, UK
D	Furosemide 40mg	LM1159	07/2012	06/2015	Wockhardt Limited, UK Wrexham, UK
E	Furosémide 40mg	12155	04/2012	04/2017	Siphal, Societe des Industries Pharmaceutiques, de Tunisie

Table 2: Chromatographic conditions of the analysis

Parameter	Condition
Mobile phase	Water: Tetrahydrofuran: Acetic acid, glacial 69.3%: 29.7%: 1%
Flow rate	1 $ml.min^{-1}$
Injection volume	10µl
Reference standard	Furosemide-PHR1057-1G
Detection wavelength	254 nm
Operating Temperature	30°C

Table 3: Appearance features of the different brands of furosemide 40 mg tablets

Parameter	Brand A	Brand B	Brand C	Brand D	Brand E
Shape & Color	Round & yellowish white	Round & white	Round & white	Round & white	Round & white
Surface texture & Convexity	Smooth & Biconvex	Smooth & Flat with beveled edges	Smooth & flat with beveled edges	Smooth & flat with beveled edges	Smooth & flat with beveled edges
Monograms & Score lines	None & double fracture	F-score line-40 & BL on the other side	F40 & score line & CP on the other side	F- score line-40 on one face	Furo-score line-40 on one side & siphat on other side
Presence of cracks & chips	None	None	None	None	None

Table 4: Average weight, % weight variation, hardness, friability, and disintegration time of furosemide tablets

Brand	Average Weight mg	Weight variation %	Hardness Kg/cm^2	Friability	Disintegration Time
A	152	±3.03	2.72	0.324	8.02min.
B	165	±4.605	6.5	0.12	1.20min.
C	160.1	±3.685	6.06	0.309	48sec.
D	158.15	±3.06	7.38	0.317	54sec
E	199	±1.508	10.6	0.08	4.39min.

Table 5: Results of microbial contamination tests for furosemide tablets

Brands	A	B	C	D	E
Aerobic bacteria (CFU/gm)	<10	<10	<10	<10	<10
Fungi (CFU/gm)	<10	<10	<10	<10	<10
E.Coli	Absent	Absent	Absent	Absent	Absent

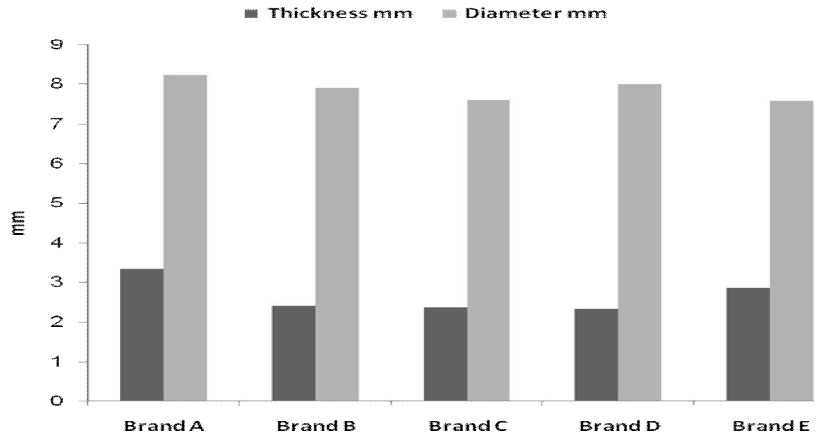

Fig. 1: Thickness and diameter (mm) of the furosemide brands

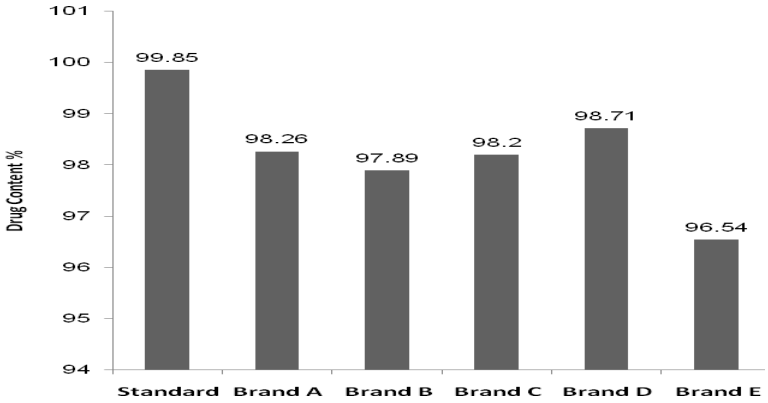

Fig. 2: Drug content of furosemide tablet brands

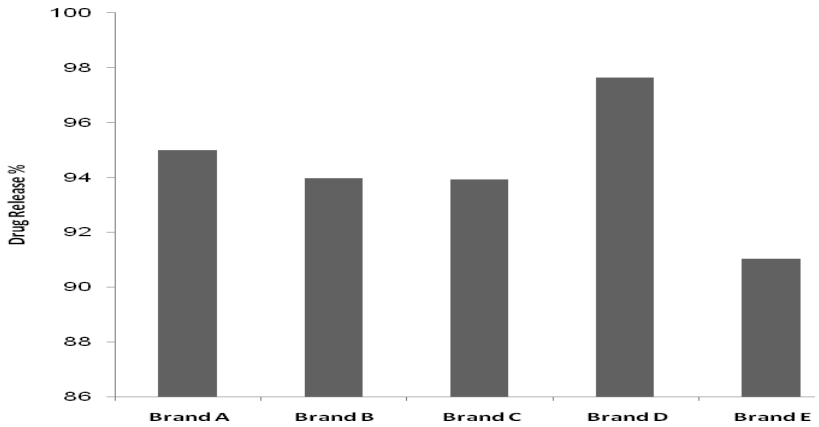

Fig. 3: Dissolution rate profiles for furosemide tablet brands at 60 minutes

REFERENCES

1. Aulton ME. Aulton's Pharmaceutics: The design and manufacture of medicines. 3rd Edn. Elsevier limited, UK; 2007.
2. Ansel HC. Introduction to pharmaceutical dosage forms. 3rdEdn. Lea & Febiger, Philadelphia. 1981.
3. Perumalla SR and Sun CC. Enabling tablet product development of 5-fluorocytosine through integrated crystal and particle engineering. J Pharm Sci. 2014;103(4): 1126-32.
4. Ansel HC, Popovich NG, Allen LV. Pharmaceutical dosage forms and drug delivery systems. 6th Edn. Williams & Wilkins, USA.1995.
5. Lajoinie A, Henin E, Kassai B and Terry D. Solid oral forms availability in children: a cost saving investigation. Br J Clin Pharmacol. 2014;78(5):1080-9.
6. Kesselheim AS, Misono AS and Lee JL. Clinical equivalence of generic and brand-name drugs used in cardiovascular diseases: A systemic review and meta-analysis. JAMA. 2008;300:2514-2526.
7. Strom BL. Generic drug substitution revisited. N Engl J Med. 1987;316:1456-1462.
8. Bamiro OA, Odeniyi MA, Idowu OB and Jaiyeoba KT. Physicochemical equivalence of chloroquine phosphate tablets. Afr J Med Med Sci. 2004;33(4):371-5.
9. El-Duah M, Ofori-Kwakye K. Substandard aretemisinin-based antimalarial medicines in licensed retail pharmaceutical outlets in Chana. J Vector Borne Dis. 2012;49(3):131-9.
10. Gackson G, Arver S, Banks I and Stecher J. Review article: Counterfeit phosphodiesterase type 5 inhibitors pose significant safety risks. Int J Clin Pract. 2010;64(4): 497-504.
11. Khuluza F. In vitro evaluation of the quality of paracetamol and co-trimoxazole tablets used in Malawi based on pharmacopeial standards. Malawi Med J. 2014;26(2):38-41.
12. Olayemi SO, Akinleye MO, Awodele EO, Idris O and Oladimeji-Salami J. The physicochemical equivalence of eight brands of amlodipine in Logos, Nigeria. West Afr J Med. 2012;31(3):154-9.
13. Akinlade B, Elkordy AA, Essa EA and Elhagar S. Liquisolid systems to improve the dissolution of furosemide. Sci Pharm. 2010;78:325-344.
14. Chella N, Narra N and Rama Rao T. Preparation and characterization of liquisolid compacts for improved dissolution of Telmisartan. Journal of Drug Delivery. 2014;2014:692793.
15. Wang T, Hoag SW, Eng ML, Polli J and Pandit NS. Quality of antiretroviral and opportunistic infection medications dispensed from developing countries and internet pharmacies. J Clin Pharm Ther. 2014.
16. Sue-chu M, Kristensen S and Tennesen HH. Photoinduced color changes in two different qualities of riboflavin in the solid state and in various tablet formulations photoreactivity of biologically active

compounds. XX. Pharmazie. 2009;64(2):428-35.
17. Yamazaki N, Tava K, Shimokawa K and Ishii F. Corrigendum to the most appropriate storage method in unit-dose package and correlation between color change and decomposition rate of aspirin tablets. Int. J Pharm. 2011;404(1-2):325-30.
18. Van der Steen KC, Frijlink HW, Schipper CMA and Barends DM. Prediction of the ease of subdivision of scored tablets from their physical parameters. AAPS PharmSciTech. 2010;11:126-132.
19. Shah RB, Collier JS, Sayeed VA, Bryant A, Habib MJ and Khan MA. Tablet splitting of a narrow therapeutic index drug: A case with levothyroxine sodium. AAPS PharmSciTech. 2010;11:1359-1367.
20. Ciurba A, Hancu G, Cojocea LM, Sipos E and Todoran N. Development of new formulation and its evaluation by capillary electrophoresis of tablets containing tramadol hydrochloride and paracetamol. Pharm Dev Technol. 2014;19(7): 833-8.
21. Järvinen MA, Paaso J and Paavola M. Continuous direct tablet compression: effects of impeller rotation rate, total feed rate and drug content on the tablet properties and drug release. Drug Dev Ind Pharm. 2013;39(11):1802-8.
22. Kushner J, Langdon BA and Hicks I. A quality-by-design study for an immediate-release tablet platform: examining the relative impact of active pharmaceutical ingredient properties, processing methods, and excipients variability on drug product quality attributes. J Pharm Sci. 2014;103(2):527-38.
23. Khan LG, Razvi N, Anjum F, Siddiqui SA and Ghayas S. Effects of various excipients on tizanidine hydrochloride tablets prepared by direct compression. Pak J Pharm Sci. 2014;27(5):1249-54.
24. Khan MQ, Razvi N, Anjum F, Ghazal L, Siddiqui SA and Ghayas S. Evaluation and comparison of different brands of domperidone tablets available in Karachi, Pakistan. Pak J Pharm Sci. 2014;27(4): 935-8.
25. Muselik J, Franc A, Dolezel P, Goněc R, Krondiová A and Lukášová I. Influence of process parameters on content uniformity of a low dose active pharmaceutical ingredient in a tablet formulation according to GMP. Acta Pharm. 2014;64(3):355-67.
26. Manek RV, Builders PF, Kolling WM, Emeje M and Kunle OO. Physicochemical and binder properties of starch obtained from Cyperus esculentus. AAPS PharmSciTech. 2012;13: 379-388.
27. Mistry AK, Nagda CD, Nagda DC, Dixit BC and Dixit RB. Formulation and in vitro evaluation of ofloxacin tablets using natural gums as binders. Sci Pharm. 2014;82(2): 441-8.
28. Melia CD and Davis SS. Review article: mechanisms of drug release from tablets and capsules.1: Disintegration. Aliment Pharmacol Ther. 1989;3(3):223-32.
29. Radwan A, Wagner M, Amidon GL and Langguth P. Bio-predictive tablet disintegration: effect of water diffusivity, fluid flow, food composition and test conditions. Eur J Pharm Sci. 2014;16(57):273-9.
30. Kasperek R, Polski A, Sobótka-Polska K and Poleszak E. Influenceof polymer type on the physical properties and the release study of papaverine hydrochloride from tablets. Polm Med. 2014;44(1):5-12.
31. Pabari RM and Ramtoola Z. Effect of a disintegration mechanism on wetting, water absorption, and disintegration time of orodispersible tablets. J Young Pharm. 2012;4:157-163.
32. Postolache L and Gafiţanu E. Comparative evaluation of the anionic superdisintegrant incorporation mode on the quality of ranitidine tablets. Rev Med Chir Soc Med Nat Iasi. 2012;116(1):336-40.
33. Melia CD and Davis SS. Review article: mechanisms of drug release from tablets and capsules.2: Dissolution. Aliment Pharmacol Ther. 1989;3(6):513-25.
34. Hammarlund MM, Paalzow LK and Odlind B. Pharmacokinetics of furosemide in man after intravenous and oral administration. Application of moment analysis. Eur J Clin Pharmacol. 1984;26:197-207.
35. Patel RC, Keraliya RA, Patel MM and Patel NM. Formulation of furosemide solid dispersion with microcrystalline cellulose for achieve rapid dissolution. J Adv Pharm Technol Res. 2010;1:180-189.

36. Akbuğa j and Gũrsoy A. Studies on Furosemide tablets I dissolutions of commercial products and different formulations. Drug Development & Industrial Pharmacy.1987;13(12):2199-2208.
37. Granero GE, Longhi MR and Mora MJ. Biowaivers monographs for immediate release solid oral dosage forms: Furosemide. J Pharm Sci. 2010;99, 2544-56.
38. Garcia-Arieta A. Interactions between active pharmaceutical ingredients and excipients affecting bioavilability: impact on bioequivalence. Eur J Pharm Sci. 2014;16(65c):89-97.
39. Kasperek R, Trębacz H, Zimmer Ł and Poleszak E. The effect of excipients on the release kinetics of diclofenac sodium and papaverine hydrochloride from composed tablet. Acta Pol Pharm. 2014;71(3):439-49.
40. Qureshi SA and Mc Gilveray IJ. Assessment of pharmaceutical quality of Furosemide tablets from multinational markets. Drug Development & Industrial Pharmacy. 1998;24(11):995-1005.