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PHARMACEUTICAL EVALUATION OF DIFFERENT TABLET BRANDS OF LETROZOLE AND IMATINIB MESYLATE MARKETED IN LIBYA

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ABSTRACT

Objectives: This study addresses pharmaceutical evaluation of different batches within two brands of two anticancer drugs, Letrozole and Imatinib mesylate tablets, that are available in Libyan drug market. Methods: Different tablet batches were subjected to in vitro evaluation for their weight variation, drug content, uniformity of dosage unit, disintegration and drug dissolution attributes. Determined quality parameters for tablet batches were then compared to their official standards stated in compendial Pharmacopoeia. Results: Inspite of the significant variations ($p< 0.05$) observed in quality parameters among tested tablet batches, all evaluated batches of Letrozole and Imatinib mesylate were found within the official specifications for weight, drug content, uniformity of dosage unit and disintegration. Dissolution studies indicated that all tested tablet batches have complied with official specifications for drug dissolution (> 80% at 30 minutes). However, in relation to Biopharmaceutical Classification System, which is a newly introduced concept and applied in regions of International Conference on Harmonization (ICH), one batch each of Letrozole and Imatinib mesylate failed the criteria for rapidly dissolving tablets that considers > 85% of drug dissolution within 30 minutes. The study concluded that batches within the evaluated brands of Letrozole and Imatinib mesylate tablets could be regarded as being biopharmaceutically and chemically equivalent and, therefore, can be interchanged in the clinical practice.

KEYWORDS: Letrozole tablets; Imatinib mesylate tablets; Pharmaceutical evaluation; quality control parameters; Libyan drug market.

INTRODUCTION

In many developing countries, introduction of generic drug products is expected to improve the overall health delivery systems[1] and the World Health Organization (WHO) has continuously advocated the use of generic brands in order to reduce the cost of medicines especially for the low income group of developing countries.[2] However, this has been associated with many problems due to the widespread distribution of fake and substandard drug products that are a major cause of morbidity, mortality, and diminished public confidence in drugs and health structures.[3,4]

About 30% of the medicines on sale for consumption in many countries in Africa and parts of Asia and Latin America are counterfeit.[5] For example, in Nigeria many generics were reported to be inequivalent to the innovated products[1,4,6,7] whereas in Tanzania, the reported treatment failure of malaria might be attributed to the poor quality of 12% of marketed antimalarials.[8,9] These reported inequivalncies highlight the importance of monitoring drug quality and were the driving strain for different drug regulatory authorities, at least in Africa, to conduct periodic market surveillance.[10]

The importance of post market evaluations of pharmaceutical products is not limited to in vitro testing of products for complaints to official specifications but also it could be used for product development or improvement of product quality.[11] Therefore, post market evaluations can be used to judge the approved products for their quality, efficacy and safety.

Therapeutics effectiveness of solid oral pharmaceutical products depends mainly on quality parameters and bioavailability of these products. On the other hand, in a series of research, we showed that quality parameters such as weight variation, disintegration, dissolution, hardness and friability are affected by drug properties, manufacturing methods and utilized excipients.[12,13] Hence, oral solid products of different manufacturers and/or sources are anticipated, like other pharmaceutical products, to measure varying quality parameters, but within permissible limits to consider as successful products. The need to ensure the pharmaceutical equivalence of generic and branded drugs products is, thus, obvious and selection of one product from several generics is always a concern issue to healthcare practitioners.[1]

Numerous works were reported on in vitro comparative evaluations of different marketed brands of aceclofenac, ciprofloxacin hydrochloride, paracetamol, ibuprofens, metformin and rifampacin tablets.[11,14-18]

Imatinib mesylate, a highly selective inhibitor of Bcr-Abl, platelet-derived growth factor receptors and c-KIT receptor tyrosine kinases,[19] is currently considered as the first line treatment for patients with newly diagnosed chronic myeloid leukemia and for the treatment of gastrointestinal stromal tumour.[20]

Letrozole, a nonsteroidal aromatase enzyme inhibitor, is used for the adjuvant treatment of different types and stages of breast cancer in postmenopausal women.[21]

As different tablet brands of Imatinib mesylate (100 and 400mg/ tablet) and Letrozole (2.5mg/ tablet) are available in Libyan drug market, the present study has been undertaken to evaluate various quality control parameters of two brands each of Imatinib 400mg and Letrozole 2.5mg tablets of different sources that marketed in Libya, aiming to evaluate the pharmaceutical and chemical equivalence of different brands in order to determine the appropriateness of the respective inter-changeability of different brands for each drug.

MATERIALS AND METHODS

Materials

The following materials were used during the experimental part of this study as described under. For Letrozole 2.5mg tablets, batches A and B (No. S0055, exp 3/ 2017 and No. S0027, exp 4/ 2016, respectively) of brand L1 in addition to batches C and D (No. 2121001, exp 10/2014 and No. 2140107, exp 1/ 2016, respectively) of brand L2 were obtained as marketed drug products from Benghazi area. For Imatinib mesylate 400mg tablets, batch E (No. S0047, exp 4/ 2014) and batch F (No. S0087, exp 8/ 2014) of brand IM1 beside batches G (No. 2131104, exp 11/ 2015) and H (No. 2120708, exp 7/ 2014) of brand IM2 were also obtained. Reference standard Letrozole and Imatinib mesylate were USP RS grade obtained from Rockville-MD and Sigma-Aldrich, USA, respectively. Acetonitrile was HPLC garde product of Fisher Scientific (United Kingdom). Other materials and reagents were analytical grade obtained from different commercial sources.

Qualification of different tablet batches

Batches with all brands were subjected to official Pharmacopoeial qualifications as stated in relevant monographs. Investigated tablet properties include weight variation, uniformity of drug content, disintegration and drug dissolution attributes.

Tablet weight variation

Only Imatinib tablet batches were subjected to the British Pharmacopeia weight variation test[22] where randomly selected 20 tablets of each tablet batch were weighed (ABS 120-4, Germany), mean value and deviations from the mean value for all tablets were calculated and compared to the allowed Pharmacoepoeial limitations. Results of the test were utilized with that of drug content to determine dosage uniformity of different Imatinib tablet batches.

Drug content for Letrozole tablets

Determination of Letrozole content in different tablet batches was conducted as per the specific USP monograph for Letrozole tablet.[23] For each batch, 10 tablets were introduced into 250ml volumetric flask and shaken with 20ml water for 5min. 75ml of Acetonitrile was then added, shaking continue to extra 30min and water was then used to complete the volume to 250ml to form sample stock solution. 20ml portion of the obtained sample stock solution was then centrifuged at 2000rpm for 5min and 1ml of supernatant was withdrawn into 20ml volumetric flask and diluted to volume with a mixture solution of Acetonitrile and water (48:52v/v). Sample solution and similarly prepared standard solution of known concentation of RS Letrozole were then injected consecutively into class-VP Autosampler HPLC (v 6.14 SPI, Shimadzu, Japan) equipped with L1 packed column (4.6-mm×12.5-cm; 5-mm) and multi wave length UV detector fixed at 230nm and a pump as described in the drug assay of the official Letrozole monograph.[23] Injected volume and flow rate were set at 20µl and 1ml/min. Peak heights corresponding to both solutions were obtained and applied to determine the content and, consequently, % of Letrozole labeled amount per tablets taken, after considering the dilution factor.

Drug content for Imatinib mesylate tablets

For Imatinib batches of tablets, drug content was conducted following the general Ph. Eur. Method 2.9.6[22] where 10 tablets, for each tablet batch, were weighed, average weight determined, crushed into fine powder and processed for Imatinib content determination using a previously reported UV method[24] after being validated as per the harmonized guidelines for single-laboratory validation of methods of analysis for detection and quantitation limits of

the drug, linearity, range, accuracy and precision.[25] Quantity of the fine powder equivalent to 10mg of Imatinib was transferred into 100 ml volumetric flask containing 30 ml distilled water, shaken manually for 10 min, volume completed with distilled water and filtered (Whatmann filter paper no. 45). 1ml of obtained filtrate is transferred to 10 ml volumetric flask, volume completed with water and the absorbance of yielded solution was measured spectrophotometrically at 281nm (UV1800 pectrophotometer, Shimadzu, Japan). Making use of generated calibration curve of RS Imatinib mesylate treated and analyzed similarly, amount of drug and % content to claimed label were thus obtained.

Dosage uniformity of Letrozole tablets

For Letrozole tablet batches, dosage uniformity test was conducted base on the content uniformity following the official USP monograph of the drug where 20 tablets from each batch were selected randomly and analyzed individually for the drug content as previously described. Values for average content, standard deviation and relative standard deviation were then calculated and compared to the Pharmacopoeial specifications for Letrozole dosage uniformity.[23]

Dosage uniformity for Imatinib mesylate tablets

Uniformity of dosage units for different Imatinib mesylate tablet batches was indicated for by the weight variation test. Tablet batches within brands of Imatinib mesylate were subjected to the official weight variation tests for film coated tablets according to official Ph. Eur. Method 2.9.5[22] using randomly selected tablets from each batch. Twenty tablets were each weighed on analytical balance and the average tablet weight was calculated. Deviation % (percent coefficient of variation, % CV) of each tablet weight from the average tablet weight was then determined and compared with the compendia specifications. Average % deviation in tablet weight was compared within batches and between brands to indicate uniformity of dosage units for Imatinib mesylate.

Tablet disintegration

Disintegration testing was performed as per method 2.9.1 described in Ph. Eur. for disintegration testing of tablets and capsules.[26] Purified water at 37 ± 2 °C was used as the test media. For each batch within the 2 examined brands of Letrozole and/or Imatinib mesylate, 6 randomly selected tablets were placed into each of the six tubes of the apparatus (Disintegration tester, Erweka, GmbH, Germany). The apparatus was operated and the time

for the last tablet to disintegrate was recorded as the disintegration time and notable observations were also recorded.

Drug dissolution of Letrozole tablets

Dissolution test of Letrozole tablets was performed according to the described USP Pharmacopeial method.[23] For each batch within brands A and B of Letrozole, 6 randomly selected tablets were placed into each of the six tubes of USP apparatus 2 (paddle) containing 500ml of 0.1N HCl equilibrated at 37±0.5^{o}C (DT-D6 Dissolution test apparatus 2, Erweka, GmbH, Germany). Paddles' rotation was set at 100rpm and test was conducted for 30min. At predetermined time intervals 10ml sample was withdrawn from each vessel, replaced with fresh medium and processed for analysis using HPLC. 200µl of each sample solution and standard solution of RS letrozole of known concentration were sequentially injected into HPLC having the same specification and conditions described in Letrozole content uniformity section. For each dissolution sample, % of Letrozole dissolved was calculated using the peak heights corresponding to drug dissolution sample and drug standard solution, concentration of drug standard solutions, label claim (mg/tablet) and volume of dissolution medium.

Drug dissolution of Imatinib mesylate tablets

Dissolution test for Imatinib mesylate tablets of different batches within the two brands was conducted according to FDA dissolution guidance.[27] For each investigated batch, 6 randomly selected tablets were placed into each of the six tubes of USP apparatus 2 (paddle) containing 1000ml of 0.1N HCl equilibrated at 37±0.5^{o}C. Paddles' rotation was set at 50rpm and test was conducted for 30min. At predetermined time intervals 5ml sample was withdrawn from each vessel and replaced with fresh medium. Collected samples were diluted to 100ml using distilled water and analyzed for the present drug spectrophotometrically at 281nm using the validated UV method that described under content uniformity test. Referring to the previously generated calibration curve of the drug, drug content and, consequently, % drug release of each dissolution sample were then obtained.

Data analysis

Data related to weight, content, disintegration and dissolution profiles of investigated tablet batches of the two drugs were presented as mean± standard deviation and compared to official limits for qualification assurance. Regression determination coefficient (r^2) was used to assess linearity association between UV absorbance and concentration of Imatinib

mesylate in order to qualify the generated calibration curve. Percent relative standard deviation (% RSD) was utilized, as a term of reference at different occasions, to validation the UV assay method of Imatinib mesylate.

Statistical analysis based on analysis of variance (ANOVA) and student t'test were used to compare weight variation, content uniformity and disintegration properties within and between different tablet batches. Statistical similarity factor (f2) was used to infer and compare Letrozole or Imatinib mesylate tablet dissolution profiles within and between each drug brands separately.

Computations were aided by STATISTICA software package and either probability $p \leq 0.05$ (with relevant comparisons) or f2 value <50 (for dissolution profiles comparison) was considered as a cutoff point for dissimilarity.

RESULTS AND DISCUSSION

Qualification of different Letrozole tablet batches

As described in method section, different Letrozole tablet batches were subjected to qualification with regard to their in vitro pharmaceutical attributes. The following subsequent sections will discuss the displayed attributes of investigated Letrozole tablet batches.

Letrozole content property

Following the official HPLC assay method of Letrozole, a well separated peak of drug was obtained at a convenient time (3.50 ± 0.03min) as a consequence of injecting 20µl of 10µg/ml USP RS Letrozole solution. Both measured tailing factor (0.96) and %RSD of drug peak height after triplicate injections (0.77%) are within the acceptable Pharmacopoeial limits for the method suitability for Letrozole assay. Displayed values for content of Letrozole among different batches investigated are varied in the range 99.6-101.2% and it appears that all tested brands are within 100 ±1.2 % of the labeled claim (Table 1). The USP specification for assay of Letrozole tablets affirms drug content per unit dosage that should not be less than 95 % and not more than 105 %.[23] Therefore, the assay results ascertain the presence of compendial content quality of Letrozole in the examined tablet batches. However, Letrozole content in tablets of batches L1-B and L2-C are significantly less ($p< 0.05$) as compared to the drug content of tablet batches L1-A or L2-D (Table I). Based on the optimal 100% content of the labeled claim, batches can be ranked as L1-A, L2-D, L2-C and L1-B.

Table 1: Drug content, content uniformity and disintegration attributes of different Letrozole tablet batches

Coded batches	Letrozole content Mean (RSD)	Content uniformity Range (RSD)	Disintegration time
L1-A	99.6 % (0.6%)	100.8 - 105.1% (2.5%)	3 min
L1-B	97.3% (1.1%)*	102.0 - 107.3% (2.3%)	4 min
L2-C	97.7% (1.9%)*	94.7 - 99.3% (2.3%)	2 min
L2-D	101.2% (1.9%)	85.8 - 96.0% (3.4%)**	1 min

**Letrozole content is significantly less (p< 0.05) compared to that of batches L1-A or L2-D.*

***Letrozole content uniformity is significantly less (p< 0.032) as compared to other batches.*

Dosage uniformity based on Letrozole content

Content uniformity of Letrozole among different tablet batches investigated varied in different ranges between 85.8-107.3% with RSD ranging from 2.3 to 3.4% (Table I). Although Letrozole batch L2-D has revealed significant less uniformity of Letrozole content (p= 0.032) as compared to other batches, all investigated tablet batches are within the permissible USP range for Letrozole tablets content uniformity (85-115% with RSD ≤ 6.0%) and none has measured a drug uniformity range greater than 100±15% of the labeled claim. Based on the tightness of the displayed content uniformity range, different batches can be ranked as L1-A, L2-C, L1-B and L2-D. In general, dosage content uniformity ensures that the tablets are within the appropriate particle size range and that both mixing and die filling during tablets manufacturing are uniform.

Letrozole tablets disintegration property

The disintegration time of tablets is known to be markedly affected by both formulation and processing variables. These variables include choice of excipients, properties of granules, mixing, lubricants used, compression force applied during tableting and the punch force time relationship.[28]

The disintegration time of Letrozole tablets within different batches varied in range from 1 to 4 minutes (Table I). In spite of the significant variation in disintegration time observed among different tablet batches (ANOVA, p <0.05), all tested batches and brands of Letrozole tablets have achieved the pharmacopoeia standard which stipulates a disintegration time of not more than 15 minutes for film coated tablets.[26] The rapid disintegration time exhibited by different tablet batches might be due to type and amount of disintegrant used in the formulations.

Generally, disintegration test measures the time required for a tablet to disintegrate into particles when in contact with gastrointestinal fluids which is a necessary condition that could be the rate-determining step in the process of drug absorption. Based on the displayed disintegration time, batches and brands of Letrozole could be ranked as L2-D, L2-C, L1-A and L1-B.

Letrozole tablets dissolution property

For a drug to be absorbed it must first dissolve in the aqueous environment of gastrointestinal tract to be absorbed. Hence, dissolution of the drug from oral solid dosage form is a necessary criterion for drug bioavailability and, consequently, dissolution testing of solid oral drug products has emerged as assuring tool for the in vivo product performance. The mean % drug dissolved at 30 minutes of different batches of Letrozole tablets vary broadly between 83.3 - 97.1% (Fig. 1 and Table 2) and such variation was shown to be considerable around the average mean of drug dissolution (ANOVA, p= 0.022). Variation in drug dissolution profiles observed in examined tablet batches is probably due to the different type and thickness of coating material that used to film coat the tablets.

Letrozole batch L2-C exhibits a significant less % of drug dissolved (83.3%, p= 0.036) in comparison to other batches. The ranking order of Letrozole tablet batches based on the time required for 50 % drug dissolution (L1-B, L1-A, L2-D and L2-C, Table 2) matches that based on % drug release at 30 minutes, which, in turn, indicates the consistency of the drug dissolution process within all batches.

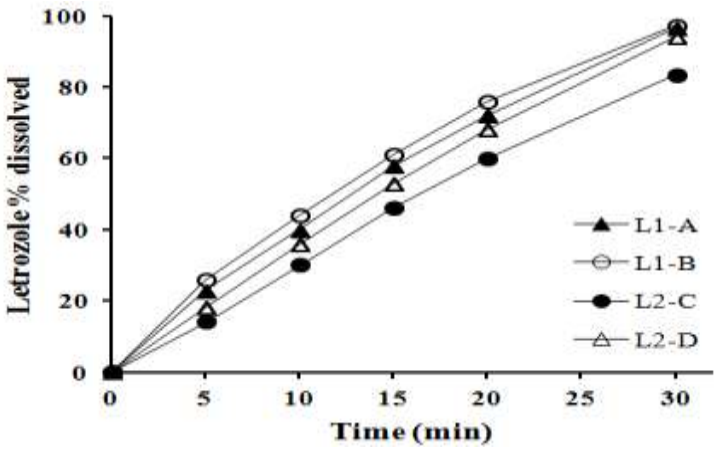

Fig. 1: Drug dissolution profiles of different Letrozole tablet batches

Table 2: Drug dissolution characteristics of different Letrozole tablet batches

Coded batches	$T_{50\%}$ [a]	% dissolved $_{30min}$	DE_{30min}
L1-A	13 ± 1 min	96.6 ±1.9 %	0.54±0.02
L1-B	12 ± 2 min	97.1 ± 1.4%	0.56 ±0.01
L2-C	17 ± 2 min	83.3 ± 3.2%*	0.44 ± 0.03**
L2-D	14 ± 1 min	95.5 ± 6.9%	0.51 ±0.04

[a] *$T_{50\%}$ stand for time for 50% drug release;* [b] *% drug dissolved in 30 minutes*

**Letrozole % release is significantly less ($p < 0.05$) compared to other batches*

***Dissolution efficiency is significantly less ($p < 0.05$) compared to other batches*

Due to the inadequacy of the percent drug release-time plot for full description of drug dissolution and/or release profile, Letrozole release data were transformed in terms of DE which incorporate an integral mode (area under release curve) suitable for correlation with tablets disintegration, if any. The concept of DE has widely considered in different fields of pharmaceutical technology.[29,30]

Values of DE for different Letrozole tablet batches are ranged 0.44-0.56 with batch L2-C exhibiting considerable less DE value as compared to other batches (Table 2). Moreover, a consistency is also observed among different batches with regard to achieved $T_{50\%}$, % $dissolved_{30min}$ and DE_{30min}. In other words, ranking order of different batches would be the same whatever dissolution parameter being used.

A poor correlation (r=0.6145, p=0.3855) is found between disintegration time and DE of different Letrozole tablet batches (Fig. 2), which, in turn, might be attributed to the free solubility of Letrozole where, in this case, tablet disintegration is expected to play a limited role in drug dissolution, as the result implies.

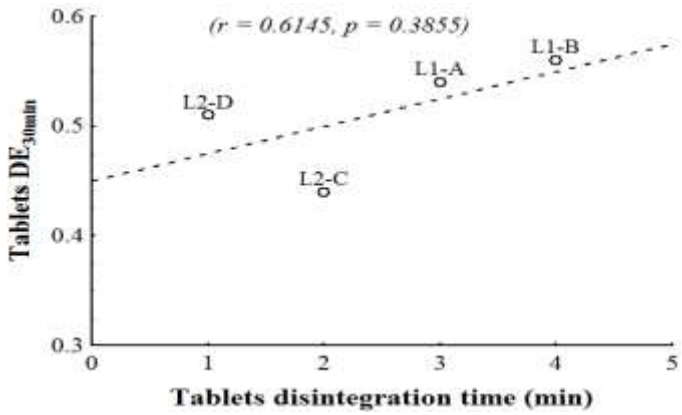

Fig. 2: Correlation profile of tablets disintegration time and drug dissolution efficiency among tested Letrozole batches.

Official USP monograph for Letrozole tablet specifies that not less than 80% of the labeled amount of the drug should dissolve within 30 min.[23] Accordingly all tested Letrozole tablet batches appear to meet the acceptance criteria for drug dissolution. However, results of similarity study which conducted to examine drug dissolution profile of different tablet batches show a significant discrepancy in Letrozole dissolution between batch L2-C and the two tablet batches of brand L1 (A and B) where comparison of drug dissolution profile of batch L2-C with either L1-A or L1-B reveal an f2 value < 50 (Table 3). This indicates that drug release profile of batch L2-C differs by 10-15% from that revealed by either L1-A or L1-B, supporting the dissimilarity of the drug dissolution profile. With an exception to batch L2-C, drug dissolution profiles of other Letrozole tablet batches appear comparable with f2 value of 56-75 for within and between brands.

Table 3: Similarity factor (f_2) and estimated equivalent difference upon comparison of drug dissolution profiles of different Letrozole tablet batches

Reference batch	Test batch	f_2	Equivalent difference
L1-A	L2-C	47	> 10%
L1-A	L2-D	68	< 5%
L1-B	L2-C	42	< 15%
L1-B	L2-D	57	< 10%
L1-A	L1-B	74	< 5%
L2-C	L2-D	56	< 10%

It should be noted, however, that among different Letrozole batches investigated, tablet batch L2-C has achieved the least % drug release at 30 min, the longest time for 50% drug dissolution and the least DE. Moreover, both statistical and f2 analysis support the inferiority of the batch with respect to drug dissolution profile. Despite that the batch L2-C has achieved the required Pharmacopoeial specifications for drug dissolution.

Interestingly, Letrozole is classified according to Biopharmaceutical Classification System (BCS) as a Class I drug and, **t**herefore, qualifies for biowaiver.[31] Based on this consideration, it is obvious then that only batches L1-A, L1-B and L2-D have met the BCS biowaiver criteria for very rapidly or rapidly dissolving tablets (> 85% of the active released within 30minutes) with batch L2-C fails to meet the same criteria.

As previously mentioned, many generic products have been evaluated for their interchangeability with innovative products using assessment of in vitro Pharmaceutical or quality control parameters of these products.[14-18] However, it is worth mentioning that this

study might be the first to address in vitro evaluation of Letrozole tablets in different brands due to the recent expiration of the patented technical information of the drug product.

Qualification of different Imatinib mesylate tablet batches

As described earlier, Imatinib mesylate tablets within all batches were evaluated for their in vitro pharmaceutical attributes. The following subsequent sections will discuss the displayed attributes of investigated tablet batches

Imatinib tablets weight property

Tablet weight of different investigated Imatinib batches vary in the range 778-783mg (Table 4) where such variation in tablet weight computed as insignificant (ANOVA, p=0.363). All tablet batches comply with the Pharmacopoeial specifications for weight variation where each tablet batch is found within the allowed 5% limit for deviation from the average tablet weight of that batch.[22] In tablets where an active ingredient constitutes more than 50% of the tablet weight (as the case with Imatinib tablets), consistency in tablet weight is an indicative parameter for uniformity of the loaded drug.

Table 4: Weight, content and dosage uniformity attributes of different Imatinib mesylate tablet batches

Coded batches	Imatinib tablet weight Mean±SD	Imatinib content Mean (SD)	Dosage uniformity [a] Range (AV)
IM1-E	782±5.0 mg	105% (1.1%)	104.4 - 107.7% (6.4)
IM1-F	780±4.2 mg	106% (1.6%)	107.2 - 111.4% (7.9)
IM2-G	783±3.8 mg	109% (0.1%)*	108.5 - 111.3% (7.4)
IM2-H	778±4.0 mg	103% (0.9%)	105.3 - 112.4% (8.4)

**Drug content is significantly higher ($p < 0.05$) compared to other batches.*

[a]Uniformity of dosage unit based on tablet weight variation where AV stands for acceptance value.

Imatinib content property

Validation of the adopted UV method for quantification of Imatining mesylate in dosage units and in dissolution samples has included linearity, sensitivity (detection and quantitation limits), precision, recovery, repeatability and reproducibility parameters. As summarized in Table 5, the attained calibration plots for standard Imatinib mesylate in solutions using the designated UV assay method show excellent linear correlation regression between drug concentration and UV absorbance with highly accepted correlation coefficients (r =0.9998) in the concentration range of 1-30µg/ml. Rregression equation that best fit for drug assay can be

read as: concentration (µg/ml) = (Absorbance - 0.0047) / 0.0202 with probability value (p) indicating the significance of the association (*p< 0.001*). Detection and quantitation limits of the assayed drug were determined as 0.04 and 0.121µg/ml, respectively. On another hand, values of relative % standard deviation associated with method repeatability and reproducibility (RSD_r and RSD_R, respectively) were < 1.2 % for a drug analyzed intra and between days with average values of recovery for intraday and between days ranged 99.7-105% for drug analysis at the three concentration levels. Moreover, displayed value of RSD_r associated with method repeatability was determine as 0.42% while values of RSD_R related to the method accuracy for drug determination at three levels were ranged as 0.19-0.28% with recovery > 99.2% (Table 5). Values of r^2, RSD_r and RSD_R associated with different technical terms assure the validity of the UV method for the assay of Imatinib mesylate in tablet batches and in dissolution samples with high precision, repeatability and reproducibility.[25]

Table 5: Properties and validation parameters of the UV assay method for Imatinib mesylate in tablet formulations and dissolution samples.

Method property	Drug levels	N	Recovery[a]	r^2	RSD_r	RSD_R
Linearity				0.9998		
Detection limit	0.04 µg/ml					
Quantitation limit	0.121 µg/ml					
Repeatability	10 µg/ml	6	99.98%		0.42%	
Accuracy	5 µg/ml	5	99.22%			0.28%
	10 µg/ml	5	100.40%			0.13%
	15 µg/ml	5	99.87%			0.19%
Intraday precision	5 µg/ml	6	99.7%		0.81%	0.22%
	15 µg.ml	6	100.4%		0.52%	0.35%
	25 µg/ml	6	101.1%		0.77%	0.42%
Between days precision	5 µg/ml	3	100.5%		0.96%	1.03%
	15 µg.ml	3	99.8%		0.76%	0.96%
	25 µg/ml	3	100.2%		0.97%	1.13%

*N, is number of analysis replicates; [a]Accuracy in calculation of the concentration obtained/actual *100%); r^2 indicates regression determination coefficient for Imatinib UV calibration curve; RSD_r and RSD_R stand for relative standard deviation under repeatability and reproducibility conditions, respectively, where RSD is (standard deviation/mean value *100%)*

Content of Imatinib mesylate among different batches investigated varied in the range 103-109% (Table VI). While % drug content of batches IM1-E, IM1-F and IM2-H appear comparable (p> 0.05), % drug content of batch IM2-G computed as significantly higher (p=

0.0262) in comparison to other batches (Table 4). It is clear that average content of Imatinib mesylate in all tested tablet batches is more than the labeled claim for drug content though within the general acceptance criteria of 100±10% of the content claim of BP for average drug content of uncoated and film coated tablets.[22] Accordingly, the result might ascertain the presence of compendial content quality of Imatinib mesylate in the examined tablet batches and based on the optimal 100% content of the labeled claim, batches can be ranked as IM2-H, IM1-E, IM1-F and IM2-G.

Imatinib tablets dosage uniformity

In accordance with BP general monograph on uncoated and film coated tablets, dosage uniformity property of Imatinib mesylate tablet within different batches is based on weight variation property rather than content uniformity criteria.[22] The test rely on concomitant determination of the drug content, average tablet mass and the relation between them aiming that the acceptance value (AV) for the relation is within the stated Pharmacopoeial limit (L1 =15).

Exhibited ranges of dosage uniformity of different Imatinib mesylate tablet batches are arrayed from 104 to 112.4% with displayed AV values of 6.4-8.4 (Table 4). No significant difference was observed in either ranges of dosage uniformity or AV values. Accordingly, all tested Imatinib tablet batches are within the specified acceptable limit for dosage uniformity as non measured AV value > 15. The results, in turn, indicate the appropriateness of adopted mixing procedure, formulation powder flow and consistency of powder filling during manufacturing of these tablet batches.

Imatinib tablets disintegration property

The disintegration time of Imatinib tablets within different batches varied between 10-12 minutes (Table 6). Moreover, no significant variation in disintegration time is observed among different tablet batches (ANOVA, p <0.112) and all tested batches and brands of Imatinib tablets have achieved the pharmacopoeia standard which stipulates a disintegration time of not more than 15 minutes for film coated tablets.[26]

Table 6: Disintegration and drug dissolution characteristics of different Imatinib mesylate tablet batches

Coded batches	Disintegration time	$T_{50\%}$ [a]	% dissolved $_{30min}$	DE_{30min}
IM1-E	10 min	18 min	81.3 ± 1.3%*	0.40±0.04*
IM1-F	11 min	17 min	91.9 ± 2.8%	0.44±0.03
IM2-G	12 min	14 min	96.1 ± 2.9%	0.51±0.03
IM2-H	10 min	15 min	93.2 ± 2.5%	0.48±0.02

[a] *$T_{50\%}$ stand for time for 50% drug release.*

* *Significantly less ($p < 0.05$) compared to other batches*

In general, a rapid disintegration time is a desired property with conventional tablets and based on the displayed disintegration time, batches and brands of Imatinib could be ranked in descending order as IM1-E, IM2-H, IM1-F and IM2-G.

Imatinib tablets dissolution property

Drug dissolution from oral conventional solid dosage forms is the most indicative in vitro parameter for the in vivo drug bioavailability, performance and therapeutic value.

The mean % drug dissolved at 30 minutes of different tablet batches of Imatinib mesylate vary between 81.3 - 96.1% (Table 6) and such variation was shown to be considerable around the average mean of drug dissolution (ANOVA, p= 0.034). Once more, observed variation in drug dissolution profiles of different tablet batches is possibly due to the different type and thickness of coating material that used to film coat the tablets.

Imatinib mesylate batch IM1-E reveals a significant less % of drug dissolved at 30 min (81.3%, p= 0.034) in comparison to other batches. As with Letrozole tablet batches, the ranking order of Imatinib mesylate tablet batches based on the time required for 50% drug dissolution (IM2-G, IM2-H, IM1-F and IM1-E, Table VII) matches that based on % drug release at 30 minutes. This, in turn, indicates the consistency of the drug dissolution process within all batches.

Where integral dissolution term is considered (DE), different Imatinib mesylate tablet batches have achieved DE values that are ranged 0.4-0.51 with batch IM1-E exhibiting a considerable less DE value among different batches investigated (Table 6). A consistency is also observed among different batches with regard to achieved $T_{50\%}$, % $dissolved_{30min}$ and DE_{30min} and different batches can be similarly ranked whatever dissolution parameter being used.

Similar to the case with Letrozole tablet batches, a poor correlation (r=0.6364, p=0.3636) is computed between disintegration time and DE of different Imatinib mesylate tablet batches (Fig. 3).

Results of similarity study which conducted to compare between drug dissolution profiles of different Imatinib mesylate tablet batches show a significant discrepancy in drug dissolution profile between batches IM1-E and IM2-G where drug release profiles of the two batches are found to differ by more than 10%, based on the attained f2 value (f2=46), supporting the dissimilarity of the drug dissolution profiles (Table 7). However, f2 values for comparison of drug release profiles among other Imatinib mesylate tablet batches are >50, indicating average differences in drug dissolution profiles account for <10%, which support the similarity of the drug dissolution profiles, within or between tested drug brands (Table 7).

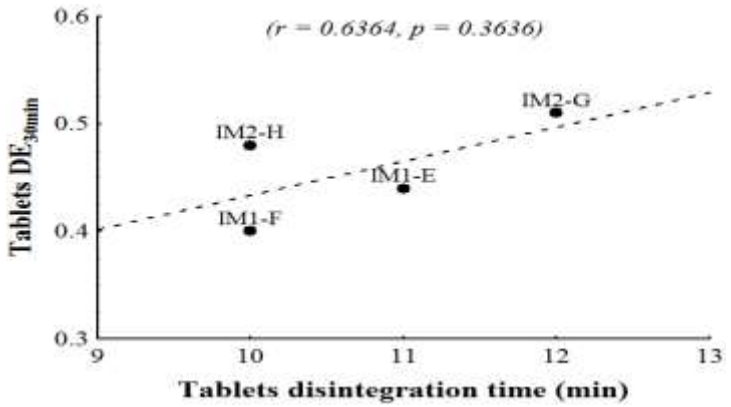

Fig. 3: Correlation profile of tablets disintegration time and drug dissolution efficiency among tested Imatinib mesylate batches.

Table 7: Similarity factor (f_2) comparison of drug dissolution profiles of different Imatinib mesylate tablet batches

Reference batch	Test batch	f_2	Average difference
IM1-E	IM2-G	46	> 10%
IM1-E	IM2-H	52	< 10%
IM1-F	IM2-G	57	< 10%
IM1-F	IM2-H	69	< 5%
IM1-E	IM1-F	62	< 10%
IM2-G	IM2-H	72	< 5%

The official BP general monograph on tablet specifies that not less than 80% of the labeled amount of the drug should dissolve within 30 min.[26] Accordingly all tested Imatinib mesylate tablet batches comply with acceptance criteria for drug dissolution.

In spite of the fact that Imatinib mesylate tablet batch IM1-E has revealed statistically proved inferiority with regard to % drug release at 30 min, time for 50% drug dissolution and DE among different Imatinib mesylate batches investigated, the batch has achieved the required Pharmacopoeial specifications for drug dissolution. However, Imatinib mesylate is classified according to Biopharmaceutical Classification System (BCS) as a Class II drug which is ineligible for biowaiver due to its pH dependent dissolution and low permeability.[32] Consequently, it is obvious then that only batches IM1-F, IM2-G and IM2-H have met the BCS criteria for very rapidly or rapidly dissolving tablets (> 85% of the active released within 30minutes) with batch IM1-E unexpectedly fails to meet the same criteria.

CONCLUSIONS

The study concludes that although one batch of Letrozole tablets and one batches of Imatinib mesylate tablets were found at the lower Pharmacopoeial limit for drug dissolution and failed to meet the dissolution requirement of the respective drug class in Biopharmaceutical classification system, all investigated tablet batches and brands of the two drugs were found to comply with the Pharmacopoeial specifications for weight variation, content, uniformity of dosage unit, disintegration and drug dissolution. Both Letrozole tablet batch L2-C and Imatinib mesylate tablet batch IM1-E show dissimilar drug dissolution profiles compared to other respective batches of each drug and, accordingly, with exception to those two batches, other batches and brands for each drug could be regarded as being pharmaceutically and chemically equivalent and can therefore be freely interchanged. The study highlighted the effectiveness of in vitro quality parameters in evaluating marketed drug products and emphasized the need of constant surveillance on marketed drug product.

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REFERENCES

1. Adegbolagun OA, Olalade OA, and Osumah SE. Comparative evaluation of the biopharmaceutical and chemical equivalence of some commercially available brands of ciprofloxacin hydrochloride tablets. Trop J Pharm Res, 2007; 6(3): 737-45.

2. World Health Organization medicines strategy; countries at the core 2004-2007. Geneva; World Health Organization (WHO): 2004 (WHO/EDM/2004.5), pp. 56-68. Available at: http:www.who.int/medicinedocs/en/d/Js5416e/
3. Counterfeit drugs: guidelines for the development of measures to combat counterfeit drugs. Geneva; World Health Organization (WHO): 1999; 1-60.
4. Taylor RB, Shakoor O, Behrens RH, Everard M, Low AS, Wangboonskul J, Reid RG, Kolawole JA. Pharmaopoeial quality of drugs supplied by Nigerian pharmacies. Lancet, 2001; 357(9272): 1933-6.
5. Technical report on counterfeit medicines: Counterfeit medicines Fact Sheet No 275. Geneva; World Health Organization (WHO): 2006.
6. Odeniyi MA, Adegoke OA, Ibitayo OB, and Jaiyeoba KT. Paracetamol Generics; a Comparative in Vitro Study. West Afr J Pharm, 2006; 19(1): 19-23.
7. Builders PF, Emeje M, and Kunle OO. Quality assessment of some commercially available piroxicam capsule in Nigeria. Nig J Pharm, 2002; 33: 28-34.
8. Petralanda I. Quality of antimalarial drugs and resistance to plasmodium vivax in Amazonian region. Lancet, 1995; 345(8962): 1433.
9. Kaur H, Goodman C, Thompson E, Thompson KA, Masanja I, Kachur SP, Abdulla S. A Nationwide survey of the Quality of Antimalarials in Retail Outlets in Tazania. PloS One, 2008; 3(10): e3403. doi: 10.1371/journal.pone.0003403. Epub 2008 Oct 15.
10. Muazu J, Gazali LK and Ogbuokiri FC. Evaluation of physicochemical properties of brands of Co-trimoxazole tablets used in antiretroviral Therapy (ART) clinic of the University of Maiduguri Teaching Hospital, North East Nigeria. W Afr J Pharm, 2008; 21(1): 8-10.
11. Chandrasekaran AR, Han CY, Chung ACY, Cheang LW, Ping LS. Post market in vitro equivalency evaluation of paracetamol tablets in kedah, Malaysia. Int J Pharm Sci Nanotech, 2011; 4(2): 1403-7.
12. Nur AO, Elamin AAG, Osman ZA, Ahmed SA. Influence of type and content of guar gum as a disintegrant and production technique on attributes of immediate release tablets. Am J Pharm Tech Res, 2014; 4(5): 546-57.
13. Nur AO, Elamin KM and Osman ZA. Individual and Mutual Effects of Applied Compression Force, Mixing Time and Manufacturing Method on Properties of HPMC Oral Matrices. World J Pharm Pharm Sci, 2015; 4(6): 1327-44.
14. Bhide MM and Nitave SA. Comparative in vitro evaluation of commercial Aceclofenac tablets. World J Pharm Pharm Sci, 2014; 3(8): 1678-87.

15. Mu'az J, Gazali LK, Sadiq GU, Tom GM. Comparative in vitro evaluation of the pharmaceutical and chemical equivalence of multi-source generic ciprofloxacin hydrochloride tablets around Maiduguri metropolitan area. Nig Journ Pharm Sci, 2009; 8(2): 102-6.
16. Giri TK and Manjusha. Comparative In Vitro Evaluation of Conventional Ibuprofen Marketed Formulation. J PharmaSciTech, 2013; 2(2): 75-80. Available at http://www.pharmascitech.in/admin/php/uploads/46_pdf.pdf
17. Olusola AM, Adekoya AI and Olanrewaju OJ. Comparative Evaluation of Physicochemical Properties of Some Commercially Available Brands of Metformin Hcl Tablets in Lagos, Nigeria. J Appl Pharm Sci, 2012; 2(2): 41-4
18. Shah SNH, Mahmood K, Uzair M, Razi MT, Rabbani M. Comparative evaluation of some commercially available brands of rifampacin tablets. J Sci Res, 2009; 38(1): 21-7
19. Petain A, Kattygnarath D, Azard J, Chatelut E, Delbaldo C, Geoerger B, Barrois M, et al. Innovative Therapies with Children with Cancer European consortium. Population pharmacokinetics and pharmacogenetics of Imatinib in children and adults. Clin Cancer Res, 2008; 14: 7102-9.
20. Kubota T. Gastrointestinal stromal tumor (GIST) and imatinib. Int J Clin Oncol, 2006; 11: 184-9.
21. Scott LJ, Keam SJ. Letrozole: in postmenopausal hormone-responsive early-stage breast cancer. Drugs, 2006; 66: 353-62. Available at http://dx.doi.org/10.2165/00003495-200666030-00010
22. British Pharmacopoeia. Volume V, Consistency of formulated preparations, London; British Pharmacopoeia Commission: 2013, Appendix XII C.
23. USP35-NF30. Letrozole tablet official monograph. United States Pharmacopoeia and National Formulary, Rockville (MD); USP Convention: 2012, pp. 3647-8. Available at: http://www.drugfuture.com/Pharmacopoeia/usp35/PDF/3647-3648%Letrozole.
24. Patil SJ, Doijad RC, Dhumal PP. Development of UV spectrophotometric method for the determination of Imatinib Mesylate (ITM) in bulk and formulation. Asian J Pharm Clin Res, 2013; 6(3): 54-7
25. Thompson M., Ellison SLR and Wood R. Harmonized guidelines for single-laboratory validation of methods of analysis, IUPAC technical report. Pure Appl Chem, 2002; 74: 835-55.

26. British Pharmacopoeia. Volume V, Disintegration and Dissolution test for tablets and capsules, London; British Pharmacopoeia Commission: 2013, Appendices XII A and XII B.
27. Guidance for dissolution methods: Imatinib Mesylate Tablets. Maryland; US Food and Drug Administration (FDA): 2013. Available at: http://www.accessdata.fda.gov/scripts/cder/dissolution/
28. Alderborn G. Tablets and compaction. In: Pharmaceutics: the science of dosage form design. Aulton ME, (ed.), 2nd edn., London; Churchill Livingstone Press: 2002, pp. 397-440.
29. Muralidhar S, Devala Rao G, Manohar Reddy B, Narayana TV, Ramesh R. Studies to enhance dissolution Profiles of Celecoxib. Int J Compre Pharm, 2011; 1(5): 1-4.
30. Chowdary KPR, Chandra DU, Parimala V, Indira, M. A factorial study on formulation development of Ibuprofen tablets employing starch 1500 and PVP K 30. Int J Pharma Sci Res, 2012; 3(1): 189-93.
31. Benet LZ. The Role of BCS (Biopharmaceutics Classification System) and BDDCS (Biopharmaceutics Drug Disposition Classification System) in Drug Development. J Pharm Sci, 2013; 102(1): 34-42.
32. Glivec® (imatinib): Drug Approval Report. Maryland; US Food and Drug Administration (FDA): 2013. Available at http://www.accessdata.fda.gov/scripts/ cder/drugsatfda/.