Comparison between Branded and Generic Furosemide 40 mg Tablets Using Thermal Gravimetric Analysis and Fourier Transform Infrared Spectroscopy

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Background and Purpose: There has been a long-standing belief that generic drugs are of lower value in comparison to their branded name counterparts. They are in particular under scrutiny due to their low market price. Even though the reduction in costs is largely based on skipping expensive preclinical studies and clinical trials for generic drugs, the purity and quality of the raw materials in the production of generic drugs is debatable. Thus, the objective of the study was to analyze and assess the quality comparability of generic furosemide 40 mg (FSD) tablets to branded product available in the market. Materials and Methods: Quality control tests, in vitro drug release assessments, and thermal analysis investigations for both analog products of FSD were performed. Various physical parameters related to the tablet quality, such as hardness, weight variation, and friability tests, were examined. In vitro drug release behavior evaluations were conducted according to United States Pharmacopeia (USP) specifications and guidelines, whereas thermal analysis was carried out using thermal gravimetric analysis (TGA), and tablets were further evaluated by Fourier transform infrared (FTIR) spectroscopy. Results: The results indicated a significant variation between the two products in terms of hardness, weight variation, and friability. This could be correlated to variation appeared in thermal and spectroscopic spectra between the two products using TGA and FTIR. Drug release of FSD was slightly different between both products following incubation in different pH media (1.2, 3.0, and 6.5; 120 min), however, this was in accordance with USP dissolution requirements as < 80% of drug release was obtained within the first 30 min from each product. Conclusion: This study is a useful example for the independent investigations using thermal and spectroscopic analysis to confirm potential hidden variations between generic and branded products that could not be obtained by the bioequivalence studies.

Keywords: Dissolution test, Fourier transform infrared spectroscopy, furosemide, quality control test, thermal gravimetric analysis, thermal analysis

INTRODUCTION

It is well known that brand and generic drugs are the two major categories of medicines in pharmaceutical market. Both are similar in terms of drug content but possibly different in their
inert ingredients and formulation features, such as color, shape, weight, method of preparations, and manufacturing process. In many countries, there is a positive attitude toward generic medicines. Public, pharmacists, and physicians consider generic medicines as a cheaper, safe equivalent alternative compared to expensive branded medicines. To approve the generic drugs for marketing, it should be interchangeable to the branded drug based on the principle known as “essential similarity.” Generic drugs should ensure that they contain the exact amount of similar active ingredient, follow a similar route of administration, and show equivalent therapeutic effectiveness as that of brand drugs. In addition, all pharmacokinetic parameters should be similar to some acceptable extent according to Food and Drug Administration (FDA) requirements, and this can be confirmed by running bioequivalence comparison studies for the active ingredients between brand and generic drugs. Lately, it has been reported that the number of prescriptions for generic over branded drugs has increased remarkably in clinical practice. At present, nearly 63% of US prescribed drugs are generic drugs due to their lower selling price as compared to brand drugs. Tens of billions of dollars every year could be saved for consumers and purchasers by choosing generic drugs. Similarly, prescriptions of generic drugs in Europe have been noticeably increased for economic reasons. Therefore, most of the healthcare providers and health insurance companies prefer prescribing generic drugs to their clients, although a controversial discussion still remains between patients regarding which one is better to use—the generics or the brands.

Many healthcare providers all over the world have taken a plan to minimize drug costs. However, some studies showed that alteration of excipients in the generic drug formulations may trigger unwanted adverse events or allergic medication reactions. Substitution of some excipients in generic drug contents has been reported to show some side effects or contraindications in certain cases that are not shown with similar branded drug. Some excipients might be of high concern with some patients when used as a substitution. For example, croscarmellose sodium in furosemide tablet has been reported to show allergic reaction in some patients. Nevertheless, croscarmellose is considered as an inert pharmaceutical excipient used in tablets as either a glidant, binder, or anti-adherent. Patients with lactose intolerance may experience gastrointestinal problems on taking generic drug with lactose in the formulation. This can affect overall absorption of the drug in gut, hence affecting the systemic drug levels. Other studies showed recurrence of some symptoms with patients on taking generic anti-arrhythmic drugs. All of the aforementioned cases were associated with generic drugs that were bioequivalent to the branded drug, hence this may indicate that bioequivalence studies are merely useful for the determination of active ingredients only. As bioavailability and bioequivalence (BAE) studies largely focus on pharmacokinetics, they do not necessarily refer to the quality of formulation. Several factors, such as composition, purity, or alteration in the preparation steps can make changes in the quality of some generic drug formulations. Heritage capsules (250 and 500 mg), the generic antibiotic tetracycline HCL, for example, was recently withdrawn from the US market because it has failed FDA dissolution specification even though it was passing the BAE studies earlier. Similar dissolution failure was also reported for the generic drug Wellbutrin (bupropion hydrochloride) which resulted in their withdrawal from the US market through the FDA.

Thermal analysis is commonly used to define the identity, quality, and purity of excipients. In particular, it is a powerful method to analyze drug-excipient interaction and stability. Alterations in the drug degradation temperature are a sign for potential interactions among the components. Furthermore, thermal analysis can help to select the optimal drug carrier ratio in the formulation. For example, differential scanning calorimetry (DSC) measurements revealed interactions of the drug naproxen with the polymer matrix. Thermal analysis can also be used to investigate the compatibility between drugs and excipients as shown for glibenclamide and ralidoxime chloride. In general, the development of other types of analytical methods such as high-performance liquid chromatography (HPLC) or liquid chromatography mass spectrometry (LC/MS) have been proven to be a challenging and time-consuming method. Therefore, thermal analysis techniques such as thermal gravimetric analysis (TGA) and DSC as well as Fourier transform infrared (FTIR) spectroscopy can be used as an easy and immediate method to scan the inactive ingredient contents in both drug types.

The rational of this study was not only to compare the active ingredient but also to include the impact of the excipients of the generic drug knowing that their type, amounts, and purity can have an influences on physicochemical properties of the final drug formulation at different extent. Alterations in stability, for example, might have an impact on the solubility and permeability behavior of the drug.
Dissolution failure with generic drug formulations of tetracycline HCL and Wellbutrin XL was reported.\(^{24,25}\)

In this work, an investigation of in vitro dissolution, quality control, and thermal analysis tests on furosemide 40mg tablets (brand vs. generic) was assessed. As expected, pH and temperature values tested were similar to the standard process applied in BABE studies, which confirmed that the proposed generic drug product not only meets the requirements but also satisfies requirements toward long-term stability and compatibility between drug and excipients. This comparison study was intended to investigate any possible changes in terms of drug release, physicochemical properties, and thermal parameters in generic drug that was claimed to be bioequivalent to branded drug.

**Materials and Methods**

**Materials**

Generic drug, furosemide 40mg tablets, and its reference product, Lasix 40mg tablets (Hoechst AG, Frankfurt, Germany), were purchased from Al Ain Pharmacy, UAE.

**Weight variation**

As stated by the United States Pharmacopeia (USP)\(^{38}\) and European Pharmacopeia,\(^{39}\) instead of content uniformity, weight variation test applies if the tablet has 25mg or more active pharmaceutical ingredient (API) or comprises 25% wt/wt. The test was implemented for illustrating the consistency of both dosage units (the declared content of FSD is 40mg per tablet). Twenty tablets were weighed from each product individually using sensitive digital balance (Shimadzu, Kyoto, Japan), and the average was calculated; deviation of average weight of tablets was confirmed by calculating percentage weight.

**Tablet friability**

Tablet friability test for each product was performed following general USP method,\(^{40}\) in which 10 tablets from each product were randomly picked, de-dusted, accurately weighed, loaded to the drum of friabilator TA 220 (Erweka), and tripped off in rotating drum (25 rpm; 4 min). Tablets were then removed from friabilator and noticed for cracks or broken edges, de-dusted to remove any free particles on tablets surface, and reweighed for calculating the weight loss percentage.

**Resistance to crushing of tablets**

Ten tablets were tested from each FSD product to investigate the resistance to crushing using hardness tester TBH-225 TD (Erweka), which simultaneously records the tablet length. Tablets were placed individually on a testing chamber with a clean horizontal surface of apparatus and aligned in such a way that the platens compress parallel to the longest axis of tablets. The mean crushing force is usually measured in Newton (N), and standard deviation was calculated for both products. Moreover, the average of tablet length and standard deviation was calculated.

**Chemical content of drug**

For chemical content determination, 20 tablets from each product were weighed and triturated to fine powder. An approximate quantity of 0.04g of the powdered material was added into 50mL distilled water. Sufficient volume of water was then added to obtain 100mL solution of drug–water mixture. This drug–water mixture solution was filtered, and the final FSD concentration of 100 µg/mL was obtained. The procedure was executed in triplicate for both products.

**Dissolution test**

In vitro drug release of FSD from each product was evaluated using dissolution apparatus 2-DT-820 (Erweka). Pedal method with 100 rpm rotational speed was used, and 900mL of different pH media, namely pH 1.2, pH 3.0, and pH 6.5, were filled with media temperature set at 37°C ± 0.5°C. Samples (10mL) were withdrawn from the dissolution vessels and replaced at the following times: 5, 10, 15, 20, 30, 45, 60, 120, and 180min. Withdrawn samples were then filtered and prepared to analyze for drug content using ultraviolet (UV) spectrophotometer (measuring at 243nm). The dissolution testing was run for six tablets. Besides, various kinetic models were used, namely first-order, zero-order, Higuchi, and Korsmeyer–Peppas model, to find the release kinetics and mechanism of drug release.\(^{41}\)

**Tablet disintegration**

Disintegration time for both FSD tablets (brand vs. generic) was determined using pharma test disintegration apparatus PTZ-Auto (Pharma Test Apparatebau, Hainburg, Germany). Distilled water was used as the disintegration media with temperature maintained at 37°C ± 0.5°C, and time duration set for 30min. Six tablets of each product were examined, and the exact time of each tablet disintegration was noted.

**Standard curve and drug content analysis**

FSD stock solutions of 0.04% wt/vol were prepared using various pH media, namely pH 1.2, pH 3, and pH 6.5. Various FSD concentrations ranging from 0.4 to 14.6 µg/mL for the calibration curves were prepared to obtain the best fit line and regression equation for further drug analysis.
Sample preparation for TGA
Samples for TGA scans were obtained by scraping the surface of the content in the liquid filled capsules. The samples were placed in a non-hermetic aluminum pans (Perkin Elmer, Beaconsfield, UK), and the lids were crimped into their place to secure the samples within. This pan was selected as it provides satisfactory contact with the samples. Thermal evaluation was conducted on both products. As a reference, an empty covered pan was used during analysis of all samples.

Thermal analysis
Thermal transition behavior of both products was investigated to measure weight difference as function of time and temperature using TGA, TGA-Q500 (Thermal Analysis Instruments, Woodland, CA, USA). In platinum pans, 15 mg of prepared samples were placed and heated up to 600°C at a rate of 5°C/min. At 5 mL/min of flow rate, nitrogen gas was purged, and the scans for each prepared sample were performed in triplicates for authentication of results.

Fourier transform infrared spectroscopy
Study was conducted using FTIR Spectrometer (Nicolet-380, Thermo Scientific, Madison, WA, USA) provisioned with attenuated total reflectance (ATR) attachment. The Thermo Smart Orbit ATR attachment was provided with a diamond crystal having single reflection in a horizontal configuration. Scanning of samples was performed with a 4 cm⁻¹ resolution from 500 to 4000 cm⁻¹, 64 times. On ATR crystal surface, 0.5 g of the sample was placed and at 20°C–22°C, spectra were collected. Background intrusion was terminated, and OMNIC Professional software, version 8.3, was used for analyzing the recorded spectra. An average of spectral data was obtained by collecting four measurements from duplicate samples.[42]

Statistical analysis
One-way analysis of variance (ANOVA) was used for comparing the mean values of determined variables for all obtained data. Differences were assessed and considered statistically significant when \( P < 0.05 \). The Minitab program (version 15.0; Minitab Inc., State College, PA, USA) was used for analysis.

RESULTS

Tablets physical quality
The results from tablet friability, variation in weight, and hardness measurement are provided in Table 1. Only the branded product met the pharmacopeial standards for weight variation and friability tests of tablets. Weight variation results showed less than 3.5% for branded tablet with a total weight of 162.7 ± 0.5 mg (1.1% ± 0.4%), but it was above 3.5% for generic tablet with a total weight of 224.1 ± 5.2 mg (5.3 ± 3.8%). This was reflected by the data obtained for percent weight loss as less lost weight for branded tablet is measured (−0.42% ± 0.07%) in comparison to generic tablet (−3.29% ± 0.5%). The mechanical strengths measured for different products were lower for generic tablet (45.6 ± 5.3 N) as compared to branded tablet (77.9 ± 8.5 N) as specified by friability and hardness test. The difference between forces required for crushing the tablets between highest mean values and lowest mean values for branded and generic tablets was approximately 78 and 46 N, respectively. ANOVA revealed significant difference among products with regard to hardness testing, weight variation, and friability \((P < 0.05)\). Tablets from both products had different tablet lengths, as generic tablet (2.89 mm) was 31.8% longer than branded tablets (1.97 mm). Regarding chemical content determination results for tested tablets of both products, content deviation was <5% from the stated amount [Table 1]. Hence, the products pass USP chemical content test, allowing a range from 90% to 110% (USP, 2016).[2] The disintegration timing for both products in 200 mL of water was less than 15 min [Table 1].

In vitro drug release evaluation
Figure 1 shows FSD release from branded and generic tablets in different pH media (pH 6.5, pH 3.0, and pH 1.2). More than 85% of FSD was released from both products in less than 30 min [Figure 1]. Hence, the products passed the standard dissolution

| Measurements                      | Generic tablet | Brand tablet |
|----------------------------------|----------------|--------------|
| Average Weight (mg)              | 224.1 ± 5.2*   | 162.7 ± 0.5  |
| Weight Variation Range (%)       | 5.3 ± 3.8*     | 1.1 ± 0.4    |
| Tablet Friability (% Weight Loss)| -3.29 ± 0.5*   | -0.42 ± 0.07 |
| Mean Resistance Force (N)        | 45.6 ± 5.3*    | 77.9 ± 8.5   |
| Mean Tablet’s Length (mm)        | 2.89 ± 0.4*    | 1.97 ± 0.9   |
| Chemical contents (%)            | 99.5 ± 0.5     | 99.9 ± 0.1   |
| Disintegrating time (min)        | 2.15 ± 0.6     | 1.30 ± 0.3   |

* p < 0.05 vs Brand tablet
test as per USP requirements for FSD tablets (i.e., \( Q < 80\% \text{ within 60 min} \)). However, drug release from both products was shown to be pH dependent. Drug release in pH 6.5 medium was considered faster than drug release in pH 3 and pH 1.2 media, respectively [Figure 2].

**Fourier transform infrared spectroscopy**

FTIR was performed on generic and branded FSD tablets products. Chemical structure of FSD is shown in Figure 3. The spectra were compared to check the presence of new bands in both samples. Any new band formation or difference can provide probability on the compatibility among the excipients in the formulations of both generic and branded FSD products. Figure 4 shows the comparison of FTIR spectra between generic and branded FSD. Both tablets showed the presence of main drug bands. The bands range of 1390–1290 cm\(^{-1}\), 1190–1120 cm\(^{-1}\), and 1060–1020 cm\(^{-1}\), which fall at the fingerprint region, were originated by S=O asymmetrical stretching, symmetrical stretching, and stretching, respectively. The peak at 1320 cm\(^{-1}\) indicated the presence of asymmetrical stretching of S=O group. The presence of primary amine of sulfonamide group bending was also indicated at 1550 cm\(^{-1}\). Two bands, namely 3400 and 3300 cm\(^{-1}\), represented N–H stretching of primary amine, confirming the presence of primary amine in FSD.

![Figure 1: Dissolution release profile of FSD for generic drug as compared to branded drug](image1.png)

![Figure 2: Dissolution release profile for branded drug as compared to generic drug at 30 min incubated in different pH media](image2.png)
**Thermal gravimetric analysis**

Figure 5 shows the results of combined TGA/Derivative Thermogravimetry (DTG) analysis of FSD from branded tablet product, whereas Figure 6 shows the results of combined TGA/DTG analysis of FSD from generic tablet product. TGA thermogram of FSD was in some way different, FSD from branded tablet showed its initial weight loss onset temperature ($T_{\text{onset}}$) at 57.04°C, whereas FSD from generic tablet showed its initial weight loss onset temperature ($T_{\text{onset}}$) at 132°C. Nevertheless, both FSD revealed approximately the same weight loss end set temperature ($T_{\text{end set}}$) [Figures 5 and 6]. Furthermore, DTG thermogram of FSD also differed in the number of endothermic decomposition peaks and temperature. As shown in Figure 5, FSD from branded tablet showed three endothermic decomposition peaks. The first two were partial decomposition peaks between 80°C–90°C and 120°C–130°C followed by third decomposition peak at 160°C. In contrast, FSD from generic tablet showed only two endothermic decomposition peaks [Figure 6], one partial decomposition peak at 150°C followed by a broad decomposition peak between 200°C and 210°C. Accordingly, these differences in either TGA or DTG analysis might correspond to different additives in the product.

**DISCUSSION**

Physical qualities, inclusive of tablets uniformity of weight and mechanical strengths, showed sufficiently good results by different FSD products [Table 1]; the latter was revealed by almost no loss from products resulting from friability testing. With advanced machinery and better quality formulation, production of tablets with an intended weight range is achievable, which usually substitutes minimum requirements of the USP.

Both tablets were simultaneously subjected to hardness test. Higher resistance to crushing strength was obtained for the brand drug which had lower tablet weight (162.7 mg) and length (197 mm) in comparison to the generic tablet (224.1 mg and 2.89 mm). Better resistance to crushing can slow down drug release from a solid unit dosage form. On the other hand, tablets with higher stability are preferable to control vibrations and following handling, inclusive of packaging, storage, transportation, and mainly the push of the tablets from its primary packaging; attentiveness is the key to cause no harm to the drug’s dissolution.
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The USP permits an extensive range of FSD (active principle) in the tablets with as high as 110% and lower range of 90% in contrast to British Pharmacopeia (BP) where the upper and lower limit are given as 105% and 95%, respectively. Regardless of the differences, in accordance with both pharmacopeial standards, all products passed the test [Table 1]. Considering the percentage of the chemical contents, that is, almost 100% for both generic and brand, comparative dissolution experiments calculating % dissolved drug are the justification for the use of labeled amount of drug instead of chemical content test.

Dissolution testing is considered as an aid to predict the in vivo bioavailability and release behavior of drugs and is being used to show bioequivalence, enabling interchangeability. Generally, FDA examines in vitro dissolution to be better perceptive than in vivo study.\textsuperscript{[46]} FSD is considered under the group IV of biopharmaceutics classification system (BCS), indicating less solubility and permeability.\textsuperscript{[47,48]} FSD is considered under the group IV of biopharmaceutics classification system (BCS), indicating poor solubility and permeability.\textsuperscript{[47,48]} Hence, the drug is not eligible for FDA bio-waiver approval.\textsuperscript{[35]} It is also concluded

Figure 5: Thermal gravimetric analysis/DTG analytical spectra of furosemide from branded tablet product

Figure 6: Thermal gravimetric analysis/DTG analytical spectra of furosemide from generic tablet product
that current regulatory guidance does not allow bio-
waivers for BCS Class IV APIs.[35] This study concealed
the tablet dissolution, including only one strength
(40 mg) oral formulation, in contrasting pH media.
Dissolution of FSD of both products was instant with
85% release of labeled amount in 20–30 min [Figure
3]. Specifications in USP 32 for FSD drug dissolution
are not 80% (Q) within 60 min in phosphate buffer in
900 mL.[49] It can be observed in Figure 2 that FSD
release showed pH-dependent behavior, as at pH 6.5,
the drug was released immediately within 20 min of
starting dissolution experiment. However, at pH 3
and pH 1.2, drug fulfills the USP requirements of
dissolution but still showed less release than at pH 6.5.
So one can say that FSD tablets (40 mg), both branded
and generic products passed the dissolution test at all
pH used. Drug release followed Hixson–Crowell model,
which describes that the drug releases from the tablets
by surface degradation via erosion.

Figure 4 shows a typical representative for the FTIR
spectral comparison between the generic and branded
FSD available products. Spectra of both formulations
signified the presence of major FSD bands. The sulfur

group gives specificity to the structure of FSD. The
symmetrical and asymmetrical stretches accountable
for SO2, appeared at the fingerprint region within band
horizon of 1190–1120 and 1390–1290 cm−1. Another
stretching observed at band range 1060–1020 cm−1
indicated S=O stretch. Peak at 1320 cm−1 specified
the asymmetrical S=O group stretching.[34] A bend at
1550 cm−1 indicated the primary amine presence in
the sulfonamide group. Moreover, peaks at 3300 and
3400 cm−1 further confirmed the presence of primary
amine in FSD by N–H stretch.[45] Peak that appeared
at 1700 cm−1 in FSD indicated carbonyl existence
due to the presence of carboxylate group. New bands did not appear or
disappear on FTIR spectra for both the sample products.
However, visible difference in the intensity between both
samples was observed owing to the presence of distinct
exciipients, signaling the drug–excipients interactions.
Both products of FSD contains alike excipients such
as talc, lactose, starch, aerosol (also known as colloidal
silicon dioxide), and magnesium stearate, besides stearic
acid that is present in generic product only. The presence
of stearic acid belonged to –CH2 groups, introducing
peaks at 2900 cm−1, whereas peak at 1700 cm−1 attributed
to the carbonyl groups stretching.[30] Main peaks for talc
were recorded as follows: at 3600–3400 cm−1 to represent
hydroxyl group vibrations linked to Si (Si–OH) and
Mg (Mg–OH),[51] and at 1050 and 680 cm−1 to indicate
stretching vibrational bands for the siloxane group
(Si–O–Si) and Si=O–Mg bond, respectively. Peaks at
1150 and 2900 cm−1 presented the C–O and C–H stretch
in starch, although a wide band at 3400 cm−1 was due
to the stretch of –OH group of starch. An evident
predictive band observed at 1100 cm−1 was an indication
of aerosol because of Si–O linkage. Prominent CH3–CH2
stretching peaks were evident for magnesium stearate
at 2900–2800 cm−1, and in the band region of 1600–
1500 cm−1, COO– group was revealed by asymmetric
stretching bands. Appearance of stretching vibrations
of –OH (hydroxyl group) bands at 3600–3400 cm−1
represented the presence of lactose, and vibrational
peaks at 1200–1100 cm−1 were due to C–O–C presence,
indicating the glucose and galactose.[52]

On the basis of TGA thermogram of FSD from
brand product [Figures 5 and 6], the initial weight
loss onset that appeared at 57°C indicated the loss
of volatile material. Hence, it was proved by the first
decomposition peak that appeared between 80°C–90°C
due to the evaporation of water present in the tablet.
This is, however, not visible in FSD from generic
product, which can be attributed to the presence of
stearic acid, which is absent in the brand-name FSD.
Containing additional hydrophobic excipient most
likely hinders the absorption of water vapor into the
tablet. FSD from generic tablets showed a strong
endothermic peak that appeared around 210°C, which
indicated the melting point of the drug. This peak,
however, was not very strong in brand-name drug
with a concomitant reduction of peak size suggesting
interactions between the drug and the excipients, but
not necessarily an incompatibility. Apart from that,
different endothermic peaks observed on both products
[Figures 5 and 6] are attributable to the excipients
melting. However, the peak shape, intensity, and the
onset temperature are not identical for both, perhaps
due to overlapping of endothermic excipients melting
peaks and the dissolution of the excipients.

CONCLUSION
Thermal variations between FSD from branded
and generic tablets were determined and supported
by variations in quality control tests. This can be
attributed either to the ingredient contents, ingredient
purity, and quality, or the manufacturing process of the
manufacturer. This study is a trendsetting example for
the independent investigations using thermal analysis
to confirm any hidden variations that could not be
shown in the bioequivalence studies.

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Conflicts of interest
There are no conflicts of interest.

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