

Letter to Editor

COMPARISON BETWEEN GENERIC DRUGS AND BRAND NAME DRUGS FROM BIOEQUIVALENCE AND THERMOEQUIVALENCE PROSPECTIVE

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ABSTRACT

The belief that generic drugs are inferior to brand name drugs has been always under debate. Especially since the price of generic drugs is generally far cheaper than brand-name drugs. Although, this is because of waiving the preclinical studies and clinical trials for the generic drug, the quality, and purity of materials used for generic drug preparation is still arguable. Thus, the objective of this overview was to find out the tolerable deviations between generic and brand name drugs which should not alter the pharmacology. Using inactive additives in the generic drug different than in the brand name drug, such as binders, glidants, diluents, anti-adherents, disintegrants or polymer carrier material and filler should not change the drug bioavailability and pharmacokinetic parameters as long as both products using the identical active ingredient(s) in equivalent amounts. Even if both drug products are bioequivalent to each other in terms of active ingredient, they are not in terms of inactive ingredients. Hence, the probability of unexpected adverse drug reaction and allergies from the generic formulation are possible, especially, when people react sensitive toward specific component. Therefore, the occasional negative response occurring upon the switch from brand-name drug to the generic drug can be attributed to intra- and inter-patient variations toward inactive ingredients. Variations toward inactive ingredients can be obtained experimentally by utilizing a proper thermoanalytical technique. As a result, thermoequivalence of generic drugs to brand name drugs can be determined based on thermal information obtained from both products. In conclusion, thermoequivalence study can be a useful tool to demonstrate any possible variation between the inactive ingredients of both products.

Keywords: Generic drug, Brand name drug, Thermoequivalence, Bioequivalence, Active materials, Inactive materials

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INTRODUCTION

Commercially, medications are either brand name drugs or generic drugs. Brand name drugs are also called innovator drug and they are these type of medications which are patented, manufactured and licensed for the first time. In contrast, generic drugs are these type of medications which are bioequivalent to the brand name drugs and have identical active ingredients but produced after patent expirations by another manufacturer [1]. Generic drugs are similar to brand-name drugs in terms of identity, strength, quality, purity, safety, potency, uses and treatment. According to US Food and Drug Administration (FDA) standards, generic drugs must have identical active ingredient, dosage form, strength, efficacy, route of administration, drug bioavailability profile and pharmacokinetic (PK) parameters similar to the brand name drug [2].

Similarly, modified release formulation of the generic drug must be bioequivalent to a modified release formulation of brand name drugs such as controlled release drug preparations [3, 4]. However, some variations in the medication formulation are accepted such as purity, inactive substances variety, color, size, shape, packaging, and labeling as long as they have no interferences. Using different inactive substances in the generic drug preparation than in the brand name drug is acceptable for the generic drug by FDA. Though, these inert additives such as fillings, flavorings, glidants, lubricants, disintegrating agents and preservatives must be listed as safe and

interference free materials in the drug composition according to the FDA safety regulations. Besides, generic drugs must follow the expiry date of the brand name drug [5].

Economically, generic drugs are less costly in production than brand name drugs and therefore, they are cheaper in the market [2]. Previous studies concluded that saving up to 10 billions of dollars every year can be achieved upon replacing brand name drug by generic drugs [6]. Another economical study reported that saving of up to 158 billions of dollars every year can be achieved [7]. This can explain the reason behind the preference of choosing generic drugs over brand name drugs in the health sector, such as hospitals, healthcare centers and health insurances [8]. Overall, generic drugs are less costly due to the avoidance of repeating many costly requirements to place brand names drugs on the market such as, preclinical studies, clinical trials, advertising, marketing, and promotion. As a result, at least 80% of prescriptions filled in the US are for generic drugs according to FDA.

Since an abbreviated system (abbreviated new drug application) that designed by the 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act) in the US is applicable for approval of generic drugs of all drugs approved after 1962 [9], hence, preclinical studies and clinical trials are not required for generic drugs FDA approval [6]. This would mainly contribute to lower the cost of generic drug production [10-11].

Table 1: Regulatory standards required by brand name drugs but not generic drugs [12]

Regulatory standards	Brand name drugs	Generic drugs
Scientific studies	Full	Bioequivalence studies
New active moiety	Required	Not Required
New indication	Required	Not Required
New dosage form	Required	Limited
New strength	Required	Not Required
Patent	Required	Not Required
Exclusive marketing	Required	Not Required

Table 1 shows the differences between brand name drugs and generic drugs in terms of regulatory standards requirement. Generic drugs can be launched in the market after the patent expiration date of brand name drug takes a place. Thus, for generic drug FDA Abbreviated New Drug Application (ANDA) is used, in which many requirements are waived in comparison to new drug applications (NDA) [12, 13].

Historically, despite providing more requirements for the drug to be accepted by the 1962 Kefauver-Harris Drug Amendments (KHDA), the US regulators did not guarantee the safety of new drugs for human consumption. In the 1980's, during the AIDS crisis, the Orphan Drug Act (ODA) was enacted in 1983 to enhance medicines development for the treatment of diseases attacking small communities. In 1984, the Hatch-Waxman Act (HWA) was enacted by the US Congress for the marketing of generic drugs. In 2010, the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was stated into law. This was an amendment to the Public Health Service Act to have an abbreviated approval method for biological products that are highly biosimilar to a FDA-approved biological product with the aim to save time, money and avoiding human or animal testing [14].

For the approval of any generic drug, bioequivalence (BE) data that match the BE data of the brand name drug is mandatory as this essentially controls the quality, efficacy, and safety of generic drugs. In BE studies, pharmacokinetics parameters and drug bioavailability of both medication using the same route of administration and the same amount of drug that given to the same number of healthy volunteers under similar experimental conditions must be comparable [8-10]. Development of sensitive and validated analytical method such as high-performance liquid chromatography (HPLC) or liquid chromatography mass spectrometry (LC/MS) for measurement of both drug concentrations in plasma is critical to get precise and accurate PK parameters and proper BE results. The development of some of these analytical methods can be challenging as it depends on the amount and chemical stability and the biopharmaceutics classification system (BCS) of drug used [15-18].

In order to achieve comparable BE data, generic drugs must be identical to brand-name drugs in terms of active ingredient, strength, dosage form, route of administration and therapeutic uses. They must meet the same batch requirements for identity, strength, purity, safety and quality, whereas manufacturing process must follow FDA's regulations and standards for good manufacturing practice [8].

According to FDA, all generic drug types even a drug with narrow therapeutics index, must be bioequivalent to brand-name drugs within an acceptance interval of 80 to 125% of the AUC (area under the concentration-time curve), which reflects the rate and extent of drug absorption at a 90% confidence interval [10]. However, some drugs with narrow therapeutics index in some countries are not

interchangeable such as digoxin and phenytoin [10]. In Europe, the legal requirements for licensing pharmaceutical products is more demanding than US, since each state has its own authority in addition to the European Medicines Agency [19, 20]. Although BE parameters for generic drugs are similar to those required by US, they are more tightened for drugs with narrow therapeutics index as the BE acceptance interval is 90.00-111.11% as well as different assessment requirements for highly variable drug products [21, 22].

A number of studies have demonstrated that replacing brand name drugs by generic drugs has no differences [20]. In contrast, adverse drug reaction was reported to be found in some patients during a trail study on replacing a brand name drug of extended carbamazepine release formulation with an equivalent generic drug, although both medications were within BE acceptable range [21]. Therefore, bioequivalence does not always correspond to therapeutic equivalence. Even though BE studies can be considered as a test for pharmacokinetics, pharmacodynamics, or comparative clinical trials depending on whether the drugs work systemically or locally [22]

Even the active ingredient does not differ between brand name drug and generic drug, other excipients, may be different and they may have contradicted effect [22] since a wide variety of excipients can be used in drug formulation [23-26]. Therefore, differences in excipients between brand-name drugs and their generic counterparts can cause problems [27] even with rational drug use [28]. For example, an allergic reaction was reported upon switching the brand name drug furosemide to the generic furosemide preparation containing croscarmellose sodium in the formulation compositions [29].

Croscarmellose is an excipient with multifunctional uses, such as suspending agent, binding agent, glidant and anti-adherent material [29]. Similarly, another allergic reaction was reported for lactose-intolerant patients upon switching from an anti-arrhythmic brand-name drug to the generic drug containing lactose in the formulation [30]. Furthermore, drug relapses in some patients were reported upon switching brand name drug Prozac to the generic fluoxetine [31]. The occurrence of unexpected effects in some generic drug formulations could be attributed to various factors, such as intra-and inter-patient variations toward additive materials, patient medical conditions [32], or alteration in the drug synthesis steps [33].

Among various analytic methods, thermal analysis is a well-established, simple and sensitive evaluation technique in pharmaceutical research and production nowadays. Differential scanning calorimetry (DSC) or thermal gravimetric analysis (TGA) can be used in separated or combined measurements. Fig. 1 shows representative TGA and DSC traces with potential thermal transitions that can occur when a sample is scanned within a predetermined temperature range and a set heating ratio.

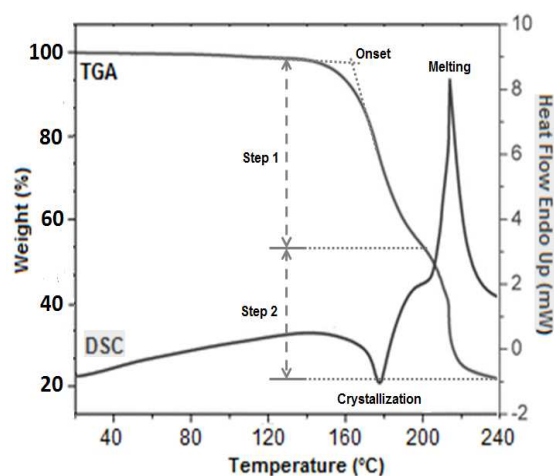


Fig. 1: Representative thermal curves of simultaneous DSC-TGA measurement

TGA analysis provides quantitative and qualitative information in form of changes in weight or energy measured as a function of time and temperature, which reflects the physical and chemical properties of the sample. In the DSC measurement, the changes in heat capacity are monitored while the sample is subjected to a controlled temperature program using a reference material. This allows the detection of changes in the heat flow such as glass and melting transition glass transitions, as well as crystallization and the associated entropies used to calculated crystallinity.

Thermal analysis has been used most widely in the pharmaceutical field to determine the identity and purity of materials. The ability to use the degradation temperature as unique characteristic to identify drugs was presented for anti-diabetic drugs, namely pioglitazone hydrochloride, rosiglitazone maleate, glibenclamide and glimepiride [34]. Thus, thermal analysis is a valuable measurement for quality control not only determining the melting temperature but also evaluating the water and ash content derived from the TGA curve as shown for terazosin hydrochloride [35] and the antihypertensive drugs Telmisartan and Cilazapril [36].

Furthermore, thermal analysis has proven to be a powerful tool in elucidating as to whether a drug and its carrier may interact when fused together or they may be stable [37] and consequently, facilitates the selection of a formulation that consists of the optimal drug carrier ratio [38]. For example, the drug-polymer interactions of naproxen and various polyethylene glycols have been investigated using DSC [39]. The compatibility of drugs with excipients is clearly reflected by intensities and shifts in thermal traces. Such potential changes were investigated for glibenclamide [40] and ralidoxime chloride using TGA and DSC, respectively [41].

Since adverse drug reaction or allergies might arise from generic formulations, thermal analysis can also be a useful tool in providing information not only on the drug but also on inactive ingredients in brand-name versus generic drugs. Potential interactions can be detected for example by a change in drug degradation temperature or number/intensities of degradation steps in the TGA traces. Changes in the DSC measurements can arise in form of different crystallization or melting temperature as well as the related entropy and crystallinity.

CONCLUSION

Even though generic drugs must be bioequivalent to brand-name drugs in terms of active ingredients, this does not mean that they are bioequivalent to each other in terms of inactive ingredients. Hence, the probability of unwanted medication reaction is possible. This might actually happen upon switching from brand name drug to generic drug. This could be attributed to intra-and inter-patient variations toward inactive ingredients. Variations toward inactive ingredients can be obtained experimentally by utilizing a proper thermoanalytical technique as thermo equivalence study can be a useful tool to demonstrate any possible variation between the inactive ingredients of both products.

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AUTHORS' CONTRIBUTION

Arafat M researched and wrote this overview. Arafat O and Ahmed Z provided guidance, critical review, and revision. All authors read and approved the final version of this comparison study.

CONFLICT OF INTERESTS

Declared none

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