



## A COMPARATIVE STUDY ON PHARMACEUTICAL EQUIVALENCE OF GENERIC AND BRANDED CARBAMAZEPINE TABLET

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### ABSTRACT

Generic drug are identical or bioequivalent to a branded drug in dosage form, safety, strength, route of administration, quality and performance characteristic and intended use. The advantage of generic drug is the low cost because they do not undergo any large expensive clinical trials like other formulations. In 2002 FDA, stated that the Americans saved 56.7 billion dollars and could save additional 1.32 billion dollars per year by using generic drugs. However, there are claims that generic drugs may differ in bioequivalence and likely to be either sub therapeutic or toxic to the patients. In our study we compared an anti epileptic drug namely, Carbamazepine generic drug with three different brand agents. Results of our study showed that individually generic drug and the branded drug complied with in the limit but dissolution, disintegration, friability, hardness test determined in pharmaceutical equivalence study showed statistically significant.

**KEYWORDS:** Generic drug, Brand name, Bioequivalence, Friability test, Hardness test.

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## INTRODUCTION

Epilepsy is a disorder characterized by recurrent seizures of cerebral origin, presenting with episodes of sensory, motor or autonomic phenomenon with or without loss of consciousness. Epilepsy is second most common neurological problem seen by the neurologist<sup>3</sup>. The prevalence rate of epilepsy was found to be 5.59 per 1000 population with no statistical difference between men and women. The world wide prevalence was found to be 4 to 10 per 1000. Incidence rate was found to be 49.3 per 100,000 and cumulative incidence is found to be 2 to 4%<sup>1, 2, 3</sup>. Mortality rate was found to be increased in the first 10 year after diagnosis<sup>3</sup>. One of the common antiepileptic drugs used is carbamazepine which has mild physiological and behavior adverse effect<sup>4</sup>. Carbamazepine belongs to class II biopharmaceutical classification system. Class II drugs have low water solubility and high permeability. The pharmacokinetic property of carbamazepine, mainly absorption depends upon the dissolution rate which indirectly correlates with bioavailability<sup>5</sup>. Bioavailability of a drug can be modified by Patient factor, Prescriber factor, Drug factor. Pharmaceutical equivalent is a drug factor which can be controlled by manufacturers to a great extent<sup>6</sup>. According to FDA, a drug product is considered to be pharmaceutically equivalents if they contain the same active ingredient(s), of the same dosage form and route of administration and are identical in strength or concentration<sup>7</sup>. Importance of pharmaceutical equivalence is, FDA considers drug products to be therapeutically equivalent only when they are pharmaceutically equivalents<sup>8</sup>.

### SCOPE OF OUR STUDY

Generic drug has shown a dramatic growth in India because of the reduction in the labour cost by 50-55% when compared to the United States and other western country. The Indian pharmaceutical market grew by 15.7% in the year 2011 and expected by 9.5% till 2015. The Indian market is expected to reach US \$72 million by 2020. Even though there is a

dramatic growth in Indian pharmaceutical market, according to WHO 3.2% of Indians fall below the poverty line and 30% of people in rural India are not affordable for the treatment due their poor economic status<sup>9</sup>. The use of generic drugs can reduce the cost for the health problems. In our present study the pharmaceutical factors of the generic drug is studied which is responsible for the alternation of bioavailability and compared with the branded carbamazepine drug. The pharmaceutical factors are determined by studying the pharmaceutical equivalence of the generic and branded carbamazepine drug. The pharmaceutical equivalence of the drug is determined by studying various parameters like Dissolution rate, Disintegration time, Friability, Hardness, Weight variation and the Active drug content which are responsible for the plasma concentration of the drug.

### METHODOLOGY

'The pharmaceutical equivalence of generic and branded carbamazepine tablet' study was presented to scientific review board of Saveetha medical college and clearance was obtained. The study was conducted in the Department of Pharmacology, Saveetha Medical College in collaboration with A TO Z pharmaceuticals. The total duration of study was six months. Group A, Group B, Group C are branded carbamazepine and Group D is generic carbamazepine is used in the study. All the selected tablets had an expiry date of more than one year. The pharmaceutical factors like Dissolution rate, Disintegration time, Friability, Weight uniformity, Hardness test, Drug content is studied.

### 1. DISSOLUTION RATE<sup>10</sup>

Eureka Dissolution Testing Instrument is used. It was carried out according to USP paddle method at stirring rate of 75rpm and the medium used is 900ml 1.0%w/v of sodium lauryl sulphate in water maintained at  $37 \pm 0.5$ °C. Withdraw a suitable volume of the medium after 60mins and filter. Suitably dilute

with fresh medium and measure the absorbance at 287nm .

### 2. DISINTEGRATION TIME<sup>11</sup>

A 900ML beaker was filled with distilled water, equilibrated to 37± or – 0.5 °c. Six tablet from each brand were subjected to test in Elchem microprocessor Based DT apparatus. Time recorded to disintegrate completely was recorded.

### 3. HARDNESS TEST<sup>12</sup>

Using a spatula, 10 tablets were individually placed between the platens of the Monsanto harness tester and their crushing strength was recorded.

### 4. FRIABILITY TEST<sup>12</sup>

Twenty tablets were randomly dusted, weighed and then placed in the drum of the Roche friabilitor. The drum was allowed to rotate for 25 rpm for 4 times. The tablets were re-dusted with soft piece of cloth and weighed. The weight loss is determined as a percentage of the initial weigh.

### 5. WEIGHT VARIATION<sup>10</sup>

10 tablets from each brand were selected, dusted and weighed individually in an Afcoset ER 18A digital balance.

### 6. DRUG CONTENT<sup>13</sup>

Assay will be repeated three times for each branded and generic carbamazepine tablets.

The result will be presented in the mean of the three determinations. Twenty randomly selected tablets from each brand were weighed and finely powdered. The drug content was determined as per Indian pharmacopeia, using the mobile phase of 30 volumes of tetra-hydro furan , 120 volumes of methanol, 80 volumes of water, 0.2ml of anhydrous formic acid, 0.5ml of tri-ethylamine and mix make up the volume upto 1000ml. Flow rate was 2ml /min , 20 micron liter loop injector and measured at 230nm.

## METIREALS AND METHODS

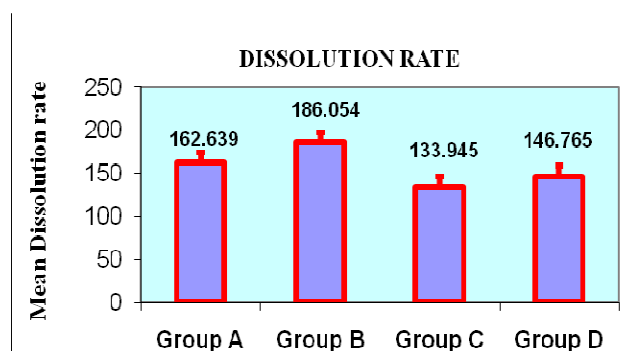
Analysis of Variance (ANOVA) is a powerful technique of testing the equality of means in more than two groups. In our study, the data was analyzed using ANOVA to test the difference in the mean levels of all groups A, B, C and D. If the difference was found to be significant, multiple comparison test (Dunnett's t) was performed comparing the groups A, B and C with the control group D. A p value of  $\leq 0.05$  was considered as statistically significant.

## RESULTS

### Dissolution rate

The descriptive analysis carried out showed that the mean values of the four groups A, B, C and D were 162.64, 166.05, 133.95 and 146.77 respectively.

**Graph 1**  
**Dissolution rate of the formulations**



Mean error bars in the graph represents mean  $\pm$  standard error of the samples along the dissolution rate.

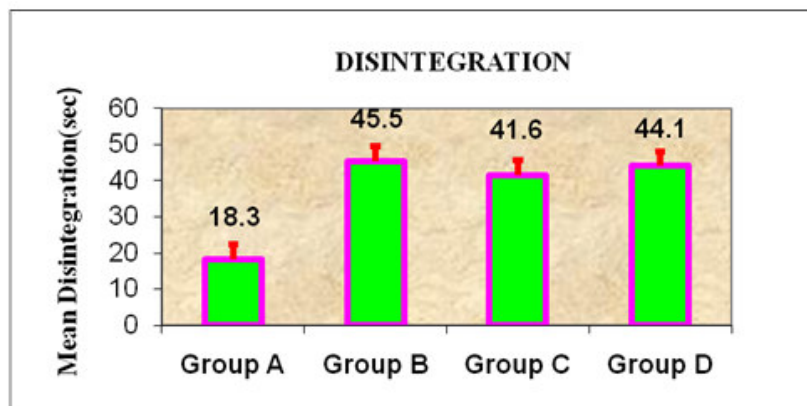
In the ANOVA performed on the mean values of the four groups, the variance ratio (F) was 51.43. This showed that the mean difference was statistically significant ( $P < 0.001$ ). The multiple comparison tests showed that the mean values of A, B and C were significantly different from group D which means the dissolution rate of branded drugs was

statistically significant from that of the generic drug.

### **Disintegration Time**

The descriptive analysis carried out showed that the mean values of the four groups A,B,C and D were 18.3,45.5,41.6 and 44.1 respectively.

**Graph 2**  
**Dissolution time of the formulations**



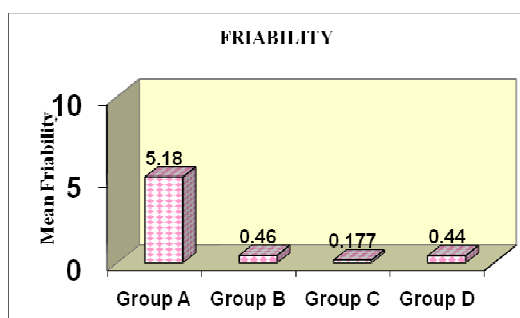
Mean error bars in the graph represent mean  $\pm$  standard error of the samples along the disintegration time. Significance of difference : $P < 0.05$ -Student t test

In the ANOVA performed on the mean values of the four groups, the variance ratio (F) was 315.113. This showed that the mean difference was statistically significant ( $P < 0.001$ ). The multiple comparison tests showed that the mean values of group A and group C were significantly different from group D which means the disintegration time of branded drugs was statistically significant from that of the generic drug. But group B was not statistically significant which means that the disintegration time of generic and brand B are more or less similar.

### **Friability**

The descriptive analysis carried out showed that the mean values of the four groups A,B,C and D were 5.18,0.46 ,0.177 and 0.44 respectively.

**Graph 3**  
**Friability of the formulations**

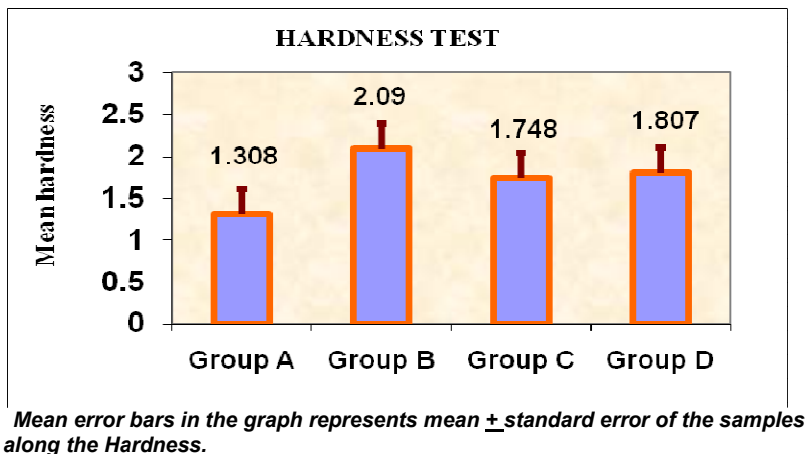


Mean error bars in the graph represents mean  $\pm$  standard error of the samples along the Friability. Significance of difference : $P < 0.05$ -Student t test

**Hardness**

The descriptive analysis carried out showed that the mean values of the four groups A,B,C and D were 1.308,2.09 ,1.748 and 1.807 respectively.

**Graph 4**  
**Hardness of the formulations**



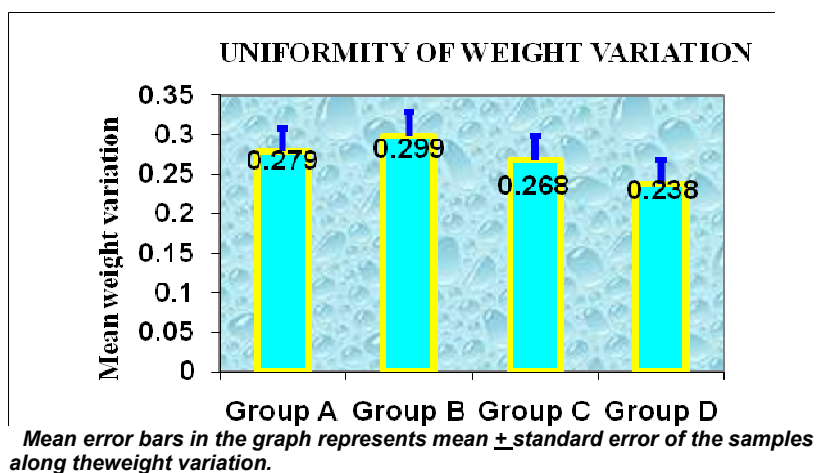
In the ANOVA performed on the mean values of the four groups, the variance ratio (F) was 9.317. This showed that the mean difference was statistically significant ( $P < 0.001$ ). The multiple comparison tests showed that the mean values of group A was significantly different from group D which means the hardness of branded drugs was statistically significant from that of the generic drug. But

group B and group C were not statistically significant which means that the hardness of generic and brand B and C are more or less similar.

**Uniformity of weight variation**

The descriptive analysis carried out showed that the mean values of the four groups A,B,C and D were 0.279,0.299,0.268 and 0.238 respectively

**Graph 5**  
**Weight variations of the formulations**



In the ANOVA performed on the mean values of the four groups, the variance ratio (F) was 427.946. This showed that the mean difference

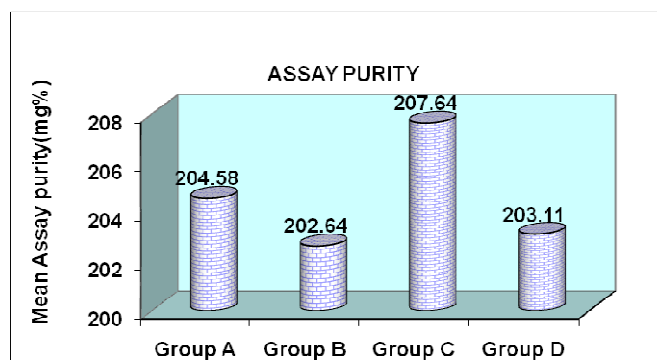
was statistically significant ( $P < 0.001$ ). The multiple comparison tests showed that the mean values of group A,B,and C were

significantly different from group D which means the weight variation of branded drugs was statistically significant from that of the generic drug.

### Drug content

The descriptive analysis carried out showed that the mean values of the four groups A,B,C and D were 1.308,2.09 ,1.748 and 1.807 respectively.

**Graph 6**  
**Assay purity of the formulations**



Mean error bars in the graph represents mean  $\pm$  standard error of the samples along the Assay purity. Significance of difference : $P < 0.05$ -Student t test

## DISCUSSION

The important objective of our study is to determine the dissolution rate, disintegration time, hardness, friability, weight variation, and the drug content of the generic and branded carbamazepine tablet. This is to make an attempt at highlighting the safety and clinical equivalence of them within the limit. The difference in these parameters can be responsible for the treatment failure or for the adverse effect<sup>12</sup> For the drugs which belong to biopharmaceutical class II, like carbamazepine, the effective surface area and the dissolution rate plays an important role. The effective surface area relates to the absorption .Tablet weight is determined by the density of the formulation components and by its proportion. There is a limit in the weight variation of the tablet. Tablet which weights between 80-250mg has a variation limit of 7.5% and tablet weight of about 500mg and above has the limit of 5%<sup>11</sup>.The average weight of the generic and the branded drug of our study complies within the limit. When the average weight of the tablet is very less this clearly indicates that either the active ingredient may be less or adequate quantity of the excipients and binders are not added to the tablet which finally affects its

manufacturing quality of the tablet and its hardness. Even though the average weight of generic tablet in our study is less when compared with other branded drugs, it was within the limit. The friability is directly related to the hardness of the tablet and the resistance to abrasion which can occur inside the end packaging or during transport or manipulation. Friability of the tablet indirectly relates the disintegration time and the dissolution rate. The tablet which is less friable disintegrates fast and the dissolution rate is also altered. Normally, weight loss of less than 1% during the friability test is the minimum requirement. And also the tablet should not show capping or cracking during such test<sup>11</sup>. The group A tablet which failed in the friability test is too brittle which may break during the transport. The friability of the generic tablet (group D) and group B was similar, when compared with group C. When the tablet is too hard it does not disintegrate in time and their dissolution rate is also varied. The hardness of the group A tablet is minimum which was confirmed in the friability test by failing in that test. The study revealed by its result, the importance of the parameters like friability, hardness, disintegration time of the

tablet in group A. Group A drug has lesser disintegration time, minimal hardness and friable. Generic tablet (group D) in hardness is more or less similar to other groups B and C. Disintegration of the tablet is the first step before the tablet goes into dissolution. Therefore the disintegration time could be related to the dissolution rate and their by the bioavailability and their therapeutic efficacy<sup>26</sup>. The disintegration time of each tablet differs. The uncoated tablet has to disintegrate within 5-30mints and for coated tablet 1-2 hrs<sup>25</sup>. In our study, we have taken an uncoated carbamazepine tablet which disintegrated with in 1 mint. The group A tablet further confirmed its hardness and friability by showing the minimum time to disintegrate. Generic tablet disintegration time was similar to that of the group B and with mild difference with group C. The dissolution rate and the disintegration time depend upon the force required to break the tablet which is determined by the compression force, concentration and type of the drug excipients which is used during the manufacturing process. Importance of dissolution rate was shown in a study were the generic 200mg carbamazepine tablet which was withdrawn from the market was correlated between the bioavailability and the in vitro dissolution rate<sup>14</sup>. A review article emphasized the FDA's concern in switching the branded and generic drug or among generic formulation. Even though the FDA has acknowledge the reports about the adverse effects of generic and the branded drug in equivalence it makes a mark that it has no conclusive evidence to show that the adverse effects are mainly due to the interchange of the generic and branded drug or vice versa. The American epilepsy society does not approve the interchange of the AED formulation without the concern of the physician and the patient and also emphasized the need of future research to associate the bio-in equivalence, therapeutic in equivalence among the generic AED formulation<sup>15</sup>. The dissolution rate of the generic drug was still higher than one of the branded drug, group C. In our study the dissolution rate of the generic

and the branded carbamazepine drugs was found to be within the limit according to United States of Pharmacopeia individually. The active drug content was determined for the generic and the branded carbamazepine drug and they were within the limits according to the pharmacopeia. The active drug content of generic drug was more or less same with group B and group A, group C was higher than generic drug. A case control study exposed the sudden unexpected death due to antiepileptic therapy found to be due to polytherapy, dose changes and high carbamazepine content<sup>16</sup>. A study also stated that, the steady state blood levels of carbamazepine of the generic and branded tablet compared, failed to correlate with seizure frequency, adverse effects<sup>17</sup>. There are also studies which showed the bioequivalence and clinical safety when two formulations were compared<sup>18,21</sup>. But at the same, there also studies where the in-vitro dissolution was correlated with the in-vivo bioavailability and the occurrence of side effects of two different formulation<sup>19, 20</sup>. Some case reports also ensured the break through seizure when there was switching of innovator drug and the generic drug<sup>22, 23, 24</sup>.

## CONCLUSION

The present study of determining the pharmaceutical equivalence of generic drug and other branded carbamazepine drug showed that they were within their limits specified by the standard pharmacopeia. The generic drug was not too inferior to the branded drug. This shows that the generic drug can be used in the place of branded drug. With the concern of the physician, the practice of generic drug usage can be encouraged in the developing countries like India in some of the conditions where the drug has to be taken for longer period. But, changing a drug from a generic to branded or vice versa without the physician concern in the treatment should not be encouraged which may affect the bioavailability and their therapeutic benefits.

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