COMPARISON OF BIOAVAILABILITY FOR PHENYTOIN PRODUCTS PREPARED BY WET GRANULATION IN NORMAL SUBJECTS AND EPILEPTIC PATIENTS*

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A 20% phenytoin (PHT) plain mixture with excipients (20%PM) and three PHT products prepared by wet granulation, which are 20% fine granule (20%FG), 99% air-dried fine granule (99%FG-A) and 99% freeze-dried fine granule (99%FG-F), were prepared. The extents of PHT absorption from these products and the Aleviatin Fine Granules® (97%FG) prepared with microcrystalline PHT powder were compared with those from commercially available PHT powder (Aleviatin®) and tablet (Hydantol Tablet 25 mg), which are of the Pharmacopoeia of Japan grade, in healthy adult volunteers.

In single dose study, the extents of PHT absorption from the powder, 20%PM, 20%FG, 99%FG-A, 99%FG-F, 97%FG and tablet were 89.7, 92.2, 99.0, 96.7, 99.1, 99.1 and 99.3%, respectively. The property of almost complete absorption of PHT from the product was shown in the 20%FG, 99%FG-F and 97%FG similar to the tablet.

In multiple dose study, the minimum and the average estimated free concentrations of PHT at steady-state for 99%FG-F and 97%FG were nearly equal to those for the tablet, and were higher than those for the powder.

In epileptic patients, the plasma PHT concentrations were increased when dosage form was changed from the powder to 99%FG-F. However, the plasma PHT concentrations were scarcely altered when dosage form was changed from the tablet to 99%FG-F. The change in dosage forms from the tablet to 99%FG-F and 97%FG or opposite direction can be done without causing toxicity in epileptic patients, so long as these products are used at the same amounts as PHT.

Keywords — phenytoin; plasma concentration; dosage form; wet granulation; freeze-drying; bioavailability; pharmacokinetics; fecal excretion

INTRODUCTION

It has been reported that the extent of phenytoin (PHT) absorption from powder form was not only lower than that of tablet form containing acid PHT in Japanese commercial sources, but also decreased upon increasing dose in therapeutic dose range in epileptic children. In the previous paper, the authors reported that the decreasing extent of PHT absorption from PHT powder was clearly demonstrated by the balance study in normal adult subjects.

Various attempts, such as size reduction of PHT crystals, conversion into amorphous form of PHT crystals, coprecipitation with polyvinylpyrrolidone, formation of β-cyclodextrin complex, and treatment with methylcellulose, to improve the bioavailability of PHT powder have been carried out. Although it has been reported that the bioavailability of these PHT preparations was higher than that of the com-

* A part of this study was presented at the 100th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1980.
merically available PHT powder, *i.e.*, raw material, none of these reports clarified whether the extent of PHT absorption from those PHT preparations is equivalent to that from the PHT tablet having the property of almost complete absorption or not.

In this study, three PHT fine granules prepared by the wet granulation and a plain mixture with excipients were prepared from one of the commercially available PHT powder preventing size alteration of PHT crystals in order to eliminate the influence of alteration in particle size of PHT on the extent of PHT absorption. The extent of PHT absorption from these products was compared with that of commercially available PHT powder, tablet, and fine granule in healthy adult subjects and epileptic patients.

MATERIALS AND METHODS

*Drugs and Subjects* — PHT powder (Aleviatin®: Dainippon Pharmaceutical Co., Ltd., Osaka) and PHT tablet (Hydantol Tablet 25 mg: Fujinaga Pharmaceutical Co., Ltd., Tokyo) were purchased from commercial sources, and were of the Pharmacopoeia of Japan (JP) grade. Aleviatin Fine Granules® (97%FG) which contained 97% of acid PHT was given from Dainippon Pharmaceutical Co., Ltd. Lactose and corn starch were commercially available and of JP grade. All other reagents were also commercially available and of analytical or reagent grade, except *n*-heptane which was of spectrophotometric grade.

Two adult subjects, one female (K. N., 35 years, 51 kg) and one male (Y.K., 31 years, 58 kg), were volunteers from the authors, and they were healthy as judged by ordinary clinical examinations. Seven epileptic out-patients undergoing antiepileptic drug therapy, five female and two male, ranging in age from 3 to 24 years, and in weight from 15 to 61 kg, participated for the study. None of them showed any sign of renal or hepatic disease in clinical examinations. They and/or their parents consented to participate in the study after the aim and protocol were explained.

*Preparation of Various PHT Products* — The PHT powder was sieved through 200 mesh screen before preparation of various PHT products.

a) 20% Plain Mixture (20%PM): One part by weight of the PHT powder and four parts by weight of excipients, which are composed of 70% of lactose and 30% of corn starch, were placed in a mortar, and were manually mixed with a pestle. The blended powders were sieved through a 100 mesh screen. The mixing and sieving were repeated two times.

b) 20% Fine Granule (20%FG): The 20%PM was manually kneaded with a minimum quantity of requirement for granulation of 4% (w/v) corn starch paste in a mortar with a pestle, was passed through a 32 mesh screen. The wet granule was dried at 40°C for 1 h and sieved through a 50 mesh screen to make the fine granule containing 20% of PHT.

c) 99% Air-dried Fine Granule (99%FG-A): One part by weight of corn starch as 4% (w/v) corn starch paste was added to 99 parts by weight of the PHT powder in a mortar, was manually kneaded with a pestle, and was passed through a 32 mesh screen. The wet granule was dried and sieved in a similar manner as 20%FG to make the fine granule containing 99% of PHT.

d) 99% Freeze-dried Fine Granule (99%FG-F): One part by weight of corn starch as 0.25% (w/v) corn starch paste was added to 99 parts by weight of the PHT powder in a flask, and was homogeneously suspended by a magnetic stirrer. The suspension was further suspended with an ultrasonic wave bath, was frozen in ethanol-dry ice bath at about -40°C, and was immediately dried in vacuo by a freeze dryer (Type 5076, Shibakagaku Co., Tokyo) with rotary vacuum pump (MCD 160, Shimadzu Corp., Kyoto). The granule was sieved through a 50 mesh screen after drying.

*Single Dose Study in a Normal Adult Subject* — The female subject K.N., who had been administered the PHT powder and tablet in single dose,2) received single oral doses of 100 mg for
20%PM, 20%FG, 99%FG-A, 99%FG-F and 97%FG in a randomized sequence. Each single oral dose study was carried out three times every two weeks. At 10 a.m., 2 h after breakfast, the subject K.N. was administered with a PHT product wrapped in a medical wafer together with about 150 ml of water.

About 6 ml of mixed saliva were drawn by the aid of mouth and tongue movement alone into plastic tubes with stopper at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 28, 32, 36, 48, 52, 56, 60, and 72 h after oral administration of PHT. The saliva samples were collected for about 5 min, and the midpoint of a sample collection period was referred to as the sampling time. The salivary pH was determined as soon as possible by a pH meter, and the saliva samples were frozen at −20°C until analyzed.

Feces were collected up to 144 h after administration of PHT. Each sample was added with about 1000 ml of 0.2 N NaOH and homogenized by a mixer for 5 min. Subsequently, it was added with 0.2 N NaOH up to 1500 or 2000 ml. A portion of the homogenized feces was kept frozen at −20°C until analyzed.

Multiple Dose Study in a Normal Adult Subject — The male subject Y.K., who had been administered the PHT powder and tablet in multiple dose,20 received the 99%FG-F and 97%FG. The subject Y.K. was administered with a product as 150 mg of PHT wrapped in a medical wafer together with about 150 ml of water at 10 a.m. and 10 p.m. for two weeks. Administration of PHT was suspended for at least three weeks between successive two runs of studies.

About 6 ml of mixed saliva was collected at 2, 4, 6, 8, 10, and 12 h after 10 a.m. dose, and at 2 and 12 h after 10 p.m. dose. After the last dose, sampling was continued at convenient times until salivary PHT concentrations became negligible. Subsequently, the saliva samples were treated in the same manner as the single dose study.

Feces were collected during PHT administration and until PHT and its metabolites became undetectable in feces after the last dose. Subsequently, each sample was treated in the same manner as the single dose study.

Clinical Application of 99%FG-F to Epileptic Patients — In seven epileptic out-patients, the dosage form was changed from the PHT powder, tablet or ground tablet to 99%FG-F without any change in coadministering antiepileptic drugs. The blood samplings were carried out before and more than four weeks after change in dosage form and/or dose of PHT. About two ml of blood samples were drawn 2−5 h after the ingestion of drugs. Each sample was immediately centrifuged and the plasma was frozen at −20°C until analyzed.

Determination Procedures of PHT Concentrations in Plasma, Mixed Saliva and Feces and of PHT Amounts in Various Products — Ultraviolet spectrophotometric methods2,8,9 were used for the determination of PHT concentration.

a) Plasma: After defrosting and mixing, 0.2 to 0.4 ml of plasma was used for the determination of total PHT concentration in plasma in epileptic patients.8

b) Mixed Saliva: After defrosting and mixing, the mixed saliva sample was centrifuged at 3000 rpm for 5 min. Two to four ml of the supernatant fluid was used for the determination of PHT concentration in the saliva.9 The estimated free concentration (Cex.b) of PHT, i.e., plasma free concentration estimated from saliva concentration by using salivary pH and the equation of Matin et al.,10 was used instead of plasma total concentration in the healthy adult subjects as previous report.2

c) Feces: After defrosting and mixing, homogenized feces was centrifuged at 3000 rpm for 5 min. One ml of supernatant fluid was added with 0.5 ml of 1 N HCl, and PHT was determined by the ultraviolet spectrophotometry incorporated with thin layer chromatography.2

d) Various Products: Each 100 mg of 20% PM, 20%FG, 99%FG-A, 99%FG-F and 97%FG was accurately weighed, put in a measuring flask, and the flask was filled up to 1000 ml with 0.01 N NaOH. One PHT tablet (25 mg/tablet) was also put in a measuring flask, and the flask
was filled up to 1000 ml with 0.01 N NaOH in a similar manner as above. After stirring for 5 min
on a magnetic stirrer, a portion of each solution was transferred to a test tube, and centrifuged
for 5 min. 0.4 ml of each supernatant fluid of 20%PM, 20%FG and tablet was taken in another
test tube. After each supernatant fluid of 99%FG-A, 99%FG-F and 97%FG was diluted five times with 0.01 N NaOH, 0.4 ml of the solution was taken in another test tube. In each case,
0.2 ml of 0.1 N HCl was added to the supernatant fluid, and PHT was determined by a similar
method for plasma.8)

Calculation of Pharmacokinetic Parameters
—Since the concentration of PHT in body fluid was sufficiently low to evoke saturation
phenomena in a single dose of PHT, the disposition of PHT was fitted by the one-compartment
open model with apparent first-order absorption and elimination except 20%PM. However, the
one-compartment open model with apparent two parallel first-order processes for absorption,
\textit{i.e.}, fairly rapid and slow absorption, and a first-order elimination was applied for the analysis of
$C_{est,f}$-time data for 20%PM similar to powder in previous report. It is also defined in this report
that $k_a$ and $k_{a2}$ are the first-order rate constants for absorption corresponding to fairly rapid
phase and slow one, respectively.

The first-order rate constants for absorption ($k_a$ and $k_{a2}$) and elimination ($k_e$) were calculated
by the method of residuals. The amount of absorption ($Df$) of PHT was obtained by subtracting
the amounts excreted in feces from dose of PHT. The total area under the $C_{est,f}$-time curve ($AUC$) was calculated by the trapezoidal rule to the last sampling time and added area to infinite
time obtained by the integration ($C_{est,f}/k_e$), where $C_{est,f}$ is the last measurement value of
$C_{est,f}$ of PHT. The apparent volume of distribution ($Vd$) was calculated according to the eq (1).

$$Vd = Df/(k_e \cdot AUC)$$  

(1)

In case of multiple dose study, the average $C_{est,f}$ value ($\bar{C}_{est,f}$) was calculated by dividing
the $AUC$ in daytime, from 10 a.m. to 10 p.m., by 12 h, and the minimum $C_{est,f}$ value ($C_{est,f \ min}$)

<table>
<thead>
<tr>
<th>Product</th>
<th>$Vd$ (l/kg)</th>
<th>$k_a$ (h$^{-1}$)</th>
<th>$k_e$ (h$^{-1}$)</th>
<th>$AUC$ (µg·h/ml)</th>
<th>Fecal excretion percent of dose of PHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder$^a$</td>
<td>5.97±0.16</td>
<td>0.25±0.05</td>
<td>0.09±0.01$^b$</td>
<td>0.068±0.007</td>
<td>4.41±0.44</td>
</tr>
<tr>
<td>20%PM</td>
<td>6.02±0.19</td>
<td>0.26±0.07</td>
<td>0.10±0.04$^b$</td>
<td>0.066±0.002</td>
<td>4.27±0.21</td>
</tr>
<tr>
<td>20%FG</td>
<td>6.00±0.10</td>
<td>0.27±0.08</td>
<td>0.067±0.002</td>
<td>4.64±0.10</td>
<td>1.0±0.3</td>
</tr>
<tr>
<td>99%FG-A</td>
<td>6.03±0.29</td>
<td>0.20±0.09</td>
<td>0.065±0.002</td>
<td>4.44±0.25</td>
<td>3.3±2.9</td>
</tr>
<tr>
<td>99%FG-F</td>
<td>5.99±0.09</td>
<td>0.43±0.09</td>
<td>0.066±0.003</td>
<td>4.70±0.04</td>
<td>0.9±0.8</td>
</tr>
<tr>
<td>97%FG</td>
<td>6.00±0.23</td>
<td>0.36±0.06</td>
<td>0.066±0.001</td>
<td>4.68±0.07</td>
<td>0.9±1.0</td>
</tr>
<tr>
<td>Tablet$^a$</td>
<td>6.01±0.28</td>
<td>0.61±0.04</td>
<td>0.067±0.005</td>
<td>4.68±0.09</td>
<td>0.7±0.7</td>
</tr>
</tbody>
</table>

Each observed value is expressed as the mean ± S.D. of three experiments. $Vd$: apparent volume of distribution, $k_a$: first-order rate constant for absorption, $k_e$: first-order rate constant for elimination, $AUC$: total area under the $C_{est,f}$-time curve.

$^a$ Data in previous report.$^{51}$ $^b$ $k_{a2}$ (see text).
was defined as the $C_{\text{est},f}$ value at 12 h after the administration, i.e., just before the next administration.

The steady-state level was defined as follows: As stated in previous report, the observed values were in a fairly good agreement with the calculated values in the simulation of $C_{\text{est},f}$-time course on multiple dose of PHT tablet in the subject Y.K. Furthermore, since the increment of the $C_{\text{est},f\min}$ value after the $n$th dose to the value after the $(n-1)$th dose became less than 1% at the 11th day after the first dose in the simulation, the $C_{\text{est},f}$-time course from the 11th day to the 14th day was defined at steady-state level. In case of PHT powder, however, the administration were continued for two days after the 14th day due to elevation of $C_{\text{est},f}$ of PHT at 12th day. Consequently, the mean value of $C_{\text{est},f\min}$ and $C_{\text{est},f}$ were obtained from the data in the last 4 d on the multiple dose study.

RESULTS

Content of PHT in Various Products

Each percent of the mean ± S.D. ($n=5$) of PHT content in tablet, 20%PM, 20%FG, 99%FG-A, 99%FG-F and 97%FG was 99.2 ± 0.02, 99.8 ± 0.02, 100.4 ± 0.02, 99.9 ± 0.02, 99.8 ± 0.01 and 99.5 ± 0.02% of the indicated amount of PHT, respectively.

Single Dose Study in a Normal Adult Subject

The pharmacokinetic parameters obtained from the $C_{\text{est},f}$-time data after the single oral administration were shown in Table I. The rate constants of absorption for 20%PM, $k_a$ and $k_{a2}$, were similar to those for PHT powder ($p>0.1$), respectively. The $k_a$ value for 20%PM was not significantly different to that for 20%FG, 99%FG-A, 99%FG-F and 97%FG ($p>0.1$) except tablet, but the $k_{a2}$ value was significantly smaller than $k_a$ for 20%FG, 99%FG-A, 99%FG-F, 97%FG and tablet ($p<0.05$).

The extents of fecal excretion of PHT were shown in Table I. The percent of PHT excreted in feces and $AUC$ values of 20%FG, 99%FG-F and 97%FG were equal to those of PHT tablet ($p>0.1$), respectively. Since PHT is thought to be neither excreted in bile nor changed in gastrointestinal tract, about 1% excretion of PHT in feces in Table I indicates that almost all quantity of PHT in those products were absorbed through gastrointestinal tract. No difference in the extent of PHT excretion in feces between 20%PM and PHT powder administration was found ($p>0.1$).

![Graph](image)
Multiple Dose Study in a Normal Adult Subject

Fig. 1 showed the $C_{\text{est.min}}$-time courses during multiple oral administration of various PHT products in the subject Y.K. The $C_{\text{est.min}}$ during multiple oral administration of various PHT products in the subject Y.K. The

### TABLE II. The Minimum and the Mean $C_{\text{est.f}}$ of Phenytoin (PHT) at Steady-State and the Extent of Fecal Excretion during Multiple Oral Administration of Various PHT Products in Subject Y.K.

<table>
<thead>
<tr>
<th>Product</th>
<th>$C_{\text{est.min}}^{b)}$ (µg/ml)</th>
<th>$C_{\text{est.f}}^{c)}$ (µg/ml)</th>
<th>Fecal excretion percent of dose of PHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder</td>
<td>0.69 ± 0.03</td>
<td>0.76 ± 0.04</td>
<td>20.3</td>
</tr>
<tr>
<td>99%FG-F</td>
<td>1.22 ± 0.04</td>
<td>1.28 ± 0.04</td>
<td>3.0</td>
</tr>
<tr>
<td>97%FG</td>
<td>1.20 ± 0.06</td>
<td>1.24 ± 0.11</td>
<td>4.2</td>
</tr>
<tr>
<td>Tablet</td>
<td>1.22 ± 0.05</td>
<td>1.30 ± 0.05</td>
<td>1.2</td>
</tr>
</tbody>
</table>

\(a)\) Data in previous report. \(b)\) The mean ± S.D. value \((n=8)\) of the minimum $C_{\text{est.f}} (C_{\text{est.min}})$ at 12 h after administration in the last 4 d on multiple dose study. \(c)\) The mean ± S.D. value \((n=4)\) of the average $C_{\text{est.f}} (C_{\text{est.f}})$ obtained by dividing the AUC in daytime (from 10 a.m. to 10 p.m.) by 12 h in the last 4 d on multiple dose study.

### TABLE III. Plasma Concentration of Phenytoin (PHT) at Steady-State in Various Dose of PHT after Chronic Administration of Powder, Tablet and 99%FG-F in Epileptic Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (year)</th>
<th>Weight (kg)</th>
<th>Dose (mg/kg/d)</th>
<th>Dosage form</th>
<th>Plasma concentration of PHT (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K.M.</td>
<td>F</td>
<td>10</td>
<td>25</td>
<td>4.0</td>
<td>Powder</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.0</td>
<td>99%FG-F</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.4</td>
<td>99%FG-F</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.0</td>
<td>99%FG-F</td>
<td>5.8</td>
</tr>
<tr>
<td>F.O.</td>
<td>F</td>
<td>6</td>
<td>18</td>
<td>4.4</td>
<td>Powder</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.4</td>
<td>99%FG-F</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.0</td>
<td>99%FG-F</td>
<td>3.3</td>
</tr>
<tr>
<td>Y.S.</td>
<td>F</td>
<td>17</td>
<td>41</td>
<td>3.7</td>
<td>Tablet</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.7</td>
<td>99%FG-F</td>
<td>2.2</td>
</tr>
<tr>
<td>I.M.</td>
<td>F</td>
<td>18</td>
<td>57</td>
<td>3.5</td>
<td>Tablet (ground)</td>
<td>13.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.5</td>
<td>99%FG-F</td>
<td>13.2</td>
</tr>
<tr>
<td>T.K.</td>
<td>F</td>
<td>24</td>
<td>61</td>
<td>3.8</td>
<td>Tablet (ground)</td>
<td>7.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.9</td>
<td>99%FG-F</td>
<td>10.7</td>
</tr>
<tr>
<td>M.K.</td>
<td>M</td>
<td>3</td>
<td>15</td>
<td>8.0</td>
<td>Powder</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.0</td>
<td>99%FG-F</td>
<td>2.9</td>
</tr>
<tr>
<td>M.N.</td>
<td>M</td>
<td>8</td>
<td>20</td>
<td>7.0</td>
<td>Powder</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.0</td>
<td>99%FG-F</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.2</td>
<td>99%FG-F</td>
<td>7.9</td>
</tr>
</tbody>
</table>
and the $C_{\text{est}}$ of PHT at steady-state, and the extent of fecal excretion of PHT were shown in Table II. It appeared that the $C_{\text{est}, \text{min}}$ and the $C_{\text{est}}$ values of 99%FG-F and 97%FG were nearly equal to those of tablet and fecal PHT excretion percent of dose of 99%FG-F and 97%FG were slightly larger than that of tablet, respectively, but smaller than that of powder in this subject to simulate the patients.

**Clinical Application of 99%FG-F to Epileptic Patients**

The plasma PHT concentrations at steady-state in various PHT doses after chronic, i.e., more than 4 weeks, administration of powder, tablet and 99%FG-F in epileptic patients were shown in Table III. In patients who switched from powder to 99%FG-F without changing dose, the plasma PHT concentrations were increased. On the other hand, the plasma PHT concentrations after changing from tablet to 99%FG-F were almost equal to those of tablet.

**DISCUSSION**

It is considered that higher bioavailability of tablet is caused by wet granulation in the manufacturing process, since the extent of absorption from the 20%FG was more excellent than that from the 20%PM in the single dose study (Table I). In other words, it is considered that an increase the wettability of PHT powder was caused by exchanging adsorbed air on the surface of PHT powder to a hydrophilic binder by wet granulation.

From these viewpoints, an attempt to coat the surface of PHT powder with a small amount of hydrophilic substance was carried out. The extent of PHT absorption from 99%FG-A prepared with 1% of corn starch paste was greater than that from PHT powder as a raw material, but lesser than that from tablet or 20%FG. While, 99%FG-F, prepared by the freeze-drying method, clearly demonstrates that PHT absorption has been improved, even by 1% of corn starch paste similar to 99%FG-A (Table I). It is reasonably considered that the surface of PHT powder was covered with pore rich layers of corn starch, the layers tend to be well wettable. On account of this notion, we are carrying out continued investigation. On the other hand, 97%FG with 3% of hydrophilic binder showed also a considerable extent of PHT absorption (Table I). These phenomena will suggest that PHT absorption in gastrointestinal tract is not only governed by dissolution rate, but by wettability as the rate-limiting step.

The nearly equal $C_{\text{est}}$ values on the average and minimum level and extent of PHT absorption to PHT tablet were obtained by dosing 99%FG-F and 97%FG in multiple dose study (Table II). Consequently, the changing in the dosage forms from tablet to 99%FG-F and 97%FG or opposite direction can be done without causing toxicity in epileptic patients. However, since the relationship between dose and plasma concentration of PHT is not proportional because of the Michaelis–Menten kinetics, 3% of difference in the dose level of PHT may cause more than 10% of difference in the PHT concentration in plasma at therapeutic range. Consequently, in the change in dosage forms from tablet to 97%FG, it is imperative to use the same amounts as PHT.

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