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Particle Size Distribution Affects the Human Bioavailability of Phenytoin

SHIGERU YAKOU,*^a SACHIKO YAMAZAKI,^b TAKASHI SONOBE,^c MASAYASU SUGIHARA,^b
KENJI FUKUMURO,^d and TSUNEJI NAGAI^e

Pharmaceutical Department, Tokyo Women's Medical College Daini Hospital,^a Nishiogu 2-1-10, Arakawa-ku, Tokyo 116, Japan, Pharmaceutical Department, Tokyo Women's Medical College,^b Kawada-cho 8-1, Shinjuku-ku, Tokyo 162, Japan, Yamanouchi Pharmaceutical Co., Ltd.,^c Ozumi 180, Yaizu-shi, Shizuoka 425, Japan, Faculty of Pharmaceutical Sciences, Science University of Tokyo,^d Ichigaya-Funakawara-machi 12, Shinjuku-ku, Tokyo 162, Japan, and Faculty of Pharmaceutical Sciences, Hoshi University,^e Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

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The particle size distributions of two commercially available batches of phenytoin (PHT) crystals were determined. Fifty-four percent of PHT crystals of one of the batches was in a large particle size range of 177—350 μm , while the other batch had a rather average particle size distribution in the range of 74—350 μm . Dissolution of the batches was tested in the JP X disintegration test medium No. 1 (pH 1.2) with 0.2% Tween 80. The apparent dissolution rate of the batch of smaller particle size was about 1.9 times faster than that of the batch of larger particle size for initial dissolution up to 30 min, but thereafter the rates became almost the same. This is because smaller particles of PHT dissolved within 30 min and dissolution thereafter was due to the larger particles in the batches. A cross-over clinical study was conducted to compare the bioavailability of these batches in humans. The area under the blood concentration-time curve (*AUC*) for the batch of smaller particle size was about 2.6 times that of the batch of larger particle size.

The present results indicate that differences in particle size distribution of PHT can cause significant differences in dissolution characteristics, especially at the initial stage of dissolution, and substantial differences in bioavailability.

Keywords—phenytoin; particle size distribution; dissolution; human cross-over study

Although it is well established that absorption of phenytoin (PHT) *in vivo* is related to the dissolution characteristics *in vitro*,^{1,2)} little is known about the detailed correlations among particle size distribution of the crystals, dissolution characteristics *in vitro* and human bioavailability of PHT.

The purpose of the present study was to investigate how much human bioavailability, as well as dissolution, may be affected by batch variation of the particle size distribution of PHT.

Experimental

Materials—PHT (JP X) was obtained from Fujinaga Pharmaceuticals Co., Ltd. (Lots BU221 and VG172A). All other chemicals used were of reagent grade.

Particle Size Distribution of PHT Crystals—The particle size distribution of PHT crystals was determined by a conventional sieving method using JIS-grade standard sieves. Ten grams of PHT was passed through 42, 80, 100, 150 and 200 mesh sieves and the residue on each sieve was weighed. The weight of each residue was divided by the total weight and multiplied by 100 to give a percentage.

Dissolution Study—Dissolution of PHT was tested in a JP X dissolution test apparatus, method II, in 500 ml of JP X disintegration test medium No. 1 (pH 1.2) with 0.2% Tween 80 at an agitation speed of 100 rpm at 37 °C. About 50 mg of PHT crystals was subjected to the test. Aliquots of 5 ml of sample solution were withdrawn at appropriate

time intervals. The sample solution was filtered through a membrane filter before ultraviolet (UV) spectrophotometry. The absorbance was determined at 235 and 260 nm and drug concentration was calculated from a previously determined calibration curve. All dissolution experiments were carried out in triplicate and the results were highly reproducible.

Human Bioavailability Study—a) Formulation and Dose: PHT crystals (50 mg) were administered orally to healthy male volunteers.

b) Subjects: A cross over study was carried out in 4 healthy male volunteers aged between 22 and 36 (mean 25) and weighing between 62 and 78 kg (mean 67.5 kg). The volunteers gave their written consent after the objective and the procedures of the trial had been explained to them. No abnormalities were found on clinical examination, in the results of hematological and biochemical profiles, or in their electrocardiograms.

c) Trial Design: The four volunteers had been fasted overnight and fasting was continued for 3 h after the dose was given with 200 ml of water. The study was single-blind and each formulation was dosed at weekly intervals and randomly allocated. Blood samples were taken by venepuncture into plastic centrifuge tubes containing heparin at 2, 4, 6, 8, 12, 24, 28, 32, 36 and 48 h after administration of the drug. The blood was immediately centrifuged and the plasma was removed.

d) Assay of the Plasma Level: The plasma samples were assayed for the drug by immunoassay.³⁾

Results and Discussion

The particle size distributions of PHT in the different batches are shown in Fig. 1. In lot VG172A, smaller particles than 105 μm amounted to 19.9% and larger ones than 177 μm amounted to 54%, and in lot BU221 particles smaller than 105 μm amounted to 27.0% and larger ones than 177 μm amounted to 40.0%. Thus, lot VG172A had more large particles than lot BU221, while lot BU221 had a rather uniform particle size distribution in the range of 74—350 μm .

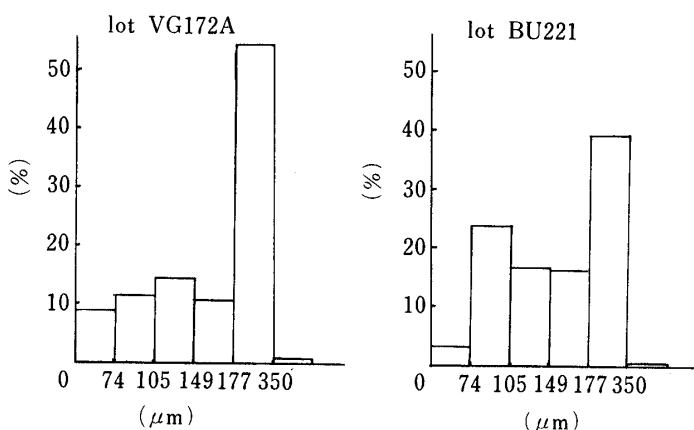


Fig. 1. Particle Size Distribution in Different Lots of Commercially Available PHT Crystals

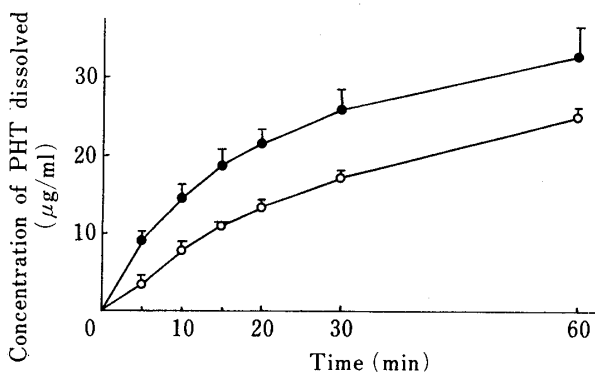


Fig. 2. Dissolution of PHT from Different Lots of Commercially Available PHT Crystals

—●—, lot BU221; —○—, lot VG172A.

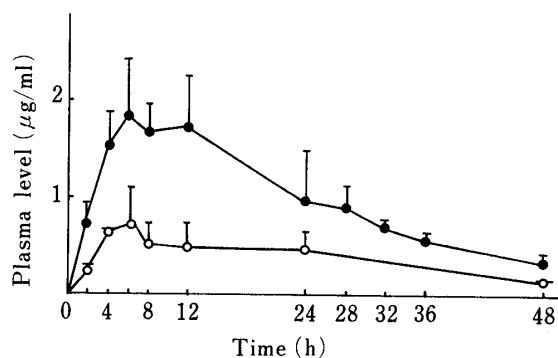


Fig. 3. Plasma Level of PHT as a Function of Time after Oral Administration of 300 mg of PHT Crystals

—●—, lot BU221; —○—, lot VG172A.

TABLE I. Comparison of AUC_{0-48h}^a Values Following the Oral Administration of PHT Crystals in the Two Batches

Sample	AUC_{0-48h}^b ($\mu\text{g}/\text{ml}\cdot\text{h}$)	Compared by the <i>t</i> -Test ^{c)}	
Lot VG172A	18.5 ± 7.7	<i>t</i> = 8.134	<i>p</i> < 0.01
Lot BU221	47.6 ± 9.7		

a) Calculated by the trapezoidal method. b) Each value is the mean ± S.D. of four males. c) $t(3, 0.01) = 5.841$. *AUC*, area under the blood concentration-time curve.

Figure 2 shows the dissolution characteristics of each batch in 500 ml of JPX disintegration test medium No. 1 (pH 1.2) containing 0.2% Tween 80. The surfactant, Tween 80, was incorporated in the test medium to improve the wetting of the crystals and accordingly to eliminate possible error arising from the initial conditions of dispersal of the crystals. The apparent initial dissolution rate of lot BU221 was 1.9 times that of lot VG172A (up to 30 min). However, thereafter the rates of dissolution became almost the same, although the cumulative concentrations of lots BU221 and VG172A were 26 and 17 $\mu\text{g}/\text{ml}$, at 30 min respectively. It is assumed that the smaller particles of PHT dissolved within 30 min and dissolution thereafter was due to the larger particles, which showed similar dissolution characteristics in both batches. Thus, the difference in particle size distribution was reflected in the dissolution characteristics, and might lead to a difference in absorption *in vivo*.

Figure 3 shows the mean plasma level of PHT in four human volunteers after oral administration of 50 mg of PHT crystals.

The values of *AUC* for the time period of 0–48 h were 47.6 ± 9.7 and $18.5 \pm 7.7 \mu\text{g}/\text{ml}\cdot\text{h}$ for lots BU221 and VG172A, respectively. The average *AUC* value (0–48 h) of PHT following the administration of lot BU221 was 2.6 ($p < 0.01$) times that of lot VG172A (Table I). The above results suggest that differences in the particle size distribution of PHT can cause significant differences in dissolution characteristics, especially at the initial stage of dissolution, and substantial differences in bioavailability.

References

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