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A New Method of Dissolution Testing for Oily Drug Preparations Using an Improved Apparatus[1)]

YOSHIHARU MACHIDA,[a] TADAKAZU TOKUMURA,*,[b] SHIGEMI KOMURO,[a] YUKI TSUSHIMA,[b] KIMIO TATSUISHI,[b] MASANORI KAYANO[b] and TSUNEJI NAGAI[a]

Faculty of Pharmaceutical Sciences, Hoshi University,[a] Ebara 2–4–41, Shinagawa-ku, Tokyo 142, Japan, and Research Center of Technological Development, Eisai Co., Ltd.,[b] Minami 2–3–14, Honjo-shi, Saitama 367, Japan

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A new method of dissolution testing for oily drug preparations, the drug and vehicles of which tend to float on the surface of the dissolution test medium, was investigated. In this study, a modified version of the paddle method of JP X, involving an additional (assistant) wing to stir the surface of the medium, was used. Moreover, polypropylene beads were added to the medium in order to enhance the efficiency of stirring. The 2nd fluid containing 20 mM sodium glycochenodeoxycholate was used as a dissolution test medium. A linear relationship was observed between the percent of the drug dissolved and the lapse of time, and also between the dissolution rate and the number of beads used. It was found that there was an optimum rotation speed of the paddle.

Keywords——*d*-α-tocopherol; sodium glycochenodeoxycholate; dissolution test medium; paddle method; bead

Dissolution testing is an important evaluation method for peroral solid preparations. In the case of a water-insoluble drug, the ordinary method of dissolution testing is inapplicable due to the problem of poor solubility of the drug in the dissolution test medium. Therefore, several modified dissolution test methods have been developed.[2–8)] These methods seemed to be useful in quality control. However, they were not effective enough to allow prediction of the bioavailability of water-insoluble drug preparations.

In the previous study,[9)] the development of a new method of dissolution testing for oily drug preparations was tried by using bile salts solution as a dissolution test medium. This dissolution test could be carried out by the paddle method using the 2nd fluid of JP X supplemented with 20 mM sodium glycochenodeoxycholate (bile salts method). However, in the case of an oily drug preparation such as a soft capsule of drug and vegetable oil as the vehicle, the drug and vehicle floated on the surface of the dissolution test medium during dissolution testing by the bile salts method, and effective dissolution was not observed. Therefore, in order to develop a method of dissolution testing for such oily drug preparations, an improvement of the dissolution test apparatus was attempted, and the factors affecting the dissolution rate in the new method of dissolution testing were investigated.

Experimental

Materials——*d*-α-Tocopherol and sodium glycochenodeoxycholate (GCDC-Na) were obtained from Eisai Co., Ltd., and Midori Chemical Co., Ltd., respectively. Other chemicals used were of reagent grade. Deionized water was used in all experiments.

Dissolution Study——The dissolution test apparatus described in JP X was improved and used. A paddle of the "paddle method" in JP X was modified in order to stir the surface of the dissolution test medium as follows; an additional (assistant) wing was attached, and the topedge of the assistant wing was adjusted to be at the surface of the dissolution test medium. Figure 1 shows the paddle with the assistant wing. In addition, polypropylene beads having

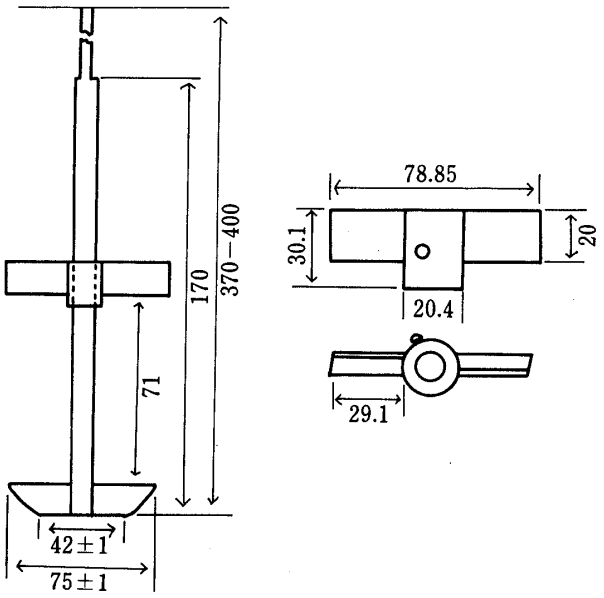

Fig. 1. The Assistant Wing Attached to the Paddle

The length unit is mm.

diameters of 4.8 mm or 3.6 mm were added to the dissolution test medium in order to enhance the stirring efficiency. This method of dissolution testing is called the "bead method" in this paper. Two different preparations, a and b, which were a tablet containing 50 mg of *d*-α-tocopherol and a soft capsule containing 100 mg of *d*-α-tocopherol, respectively, were used as model preparations. These preparations, a and b, were of the same type as preparations C and D in the previous study,[9] respectively. The dissolution test medium was made up by adding 20 mmol of GCDC-Na to 1000 ml of the 2nd fluid of JP X. The dissolution test was done with 1000 ml or 950 ml of the dissolution test medium at 37±0.5°C. The rotation speed of the paddle was 50, 75, 100, 125 or 150 rpm. A 10 ml aliquot of the sample solution was taken out and filtered through a disposable filter (Acrodisc®, 0.2 μm, German Co., Ltd.) at appropriate intervals. The concentration of *d*-α-tocopherol was determined by the ultraviolet absorption method using a Hitachi UV-200 spectrophotometer.

Results and Discussion

Dissolution of *d*-α-Tocopherol in the Bead Method

Figure 2 shows the results of dissolution tests on preparations a and b. The dissolution of *d*-α-tocopherol form preparation b was not observed in the bile salts method, in agreement with the previous result.[9] In the bead method, the dissolution of *d*-α-tocopherol from preparation b was observed, and the percent dissolved of preparation b at 4 h in the bead method was similar to that of preparation a at 4 h in the bile salts method. This results indicates that the improvement of apparatus produces an enhancement of dissolution from preparation b and that the bead method was worthy of further detailed study. Therefore, the number of beads and the paddle rotation speed were investigated as factors affecting the dissolution rate.

Effect of Number of Beads on Dissolution Rate in the Bead Method

Figure 3 shows the effect of the number of beads on the dissolution rate. At each number of beads, the relationship between time and percent dissolved was linear in the region under 80%. This result apparently indicates that the dissolution of drug occurred from a constant surface area of drug controlled by the number of beads. The slope of each straight line can be regarded as the dissolution rate of *d*-α-tocopherol. Figure 4 shows the linear relationship between the lapse of time and the dissolution rate calculated from the straight lines in Fig. 3. From the data obtained with a number of beads ranging from 300 to 2000, the following equation was obtained by the least-squares method; $Y=0.01512X+3.506$ ($r=0.9794$). The Y intercept was very close to 1.53, which was the dissolution rate in the absence of beads. It was found from these results that the dissolution rate of the drug depended on the number of

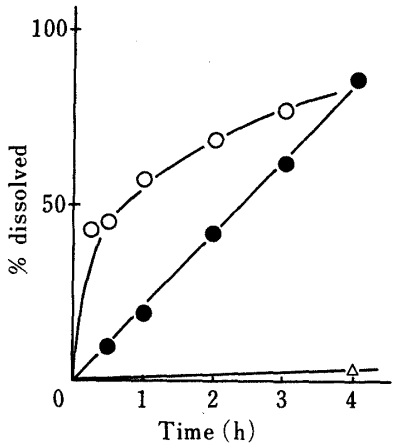

Fig. 2. Dissolution Rate of *d*-α-Tocopherol from Its Preparations in the Bile Salts and Bead Methods

○, preparation a (bile salts method); △, preparation b (bile salts method); ●, preparation b (the bead method).

Each point represents the mean of three determinations. Conditions of dissolution test: dissolution test medium, 1000 ml; rotation speed of paddle, 100 rpm; number of beads, 900.

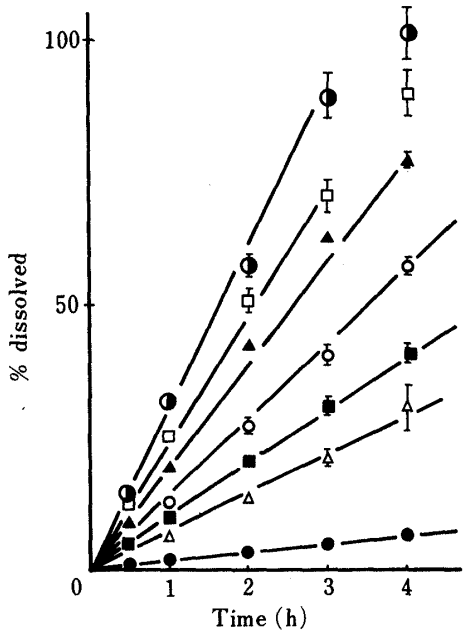

Fig. 3. Effect of Number of Beads on the Dissolution Rate of *d*-α-Tocopherol from Preparation b

Number of beads: (●) 0, (△) 300, (■) 500, (○) 700, (▲) 900, (□) 1500, (◑) 2000.

Each point represents the mean ± S.E. of three determinations. Conditions of dissolution test: dissolution test medium, 1000 ml or 950 ml (for numbers of beads above 1000); rotation speed of paddle, 100 rpm; diameter of bead, 4.8 mm.

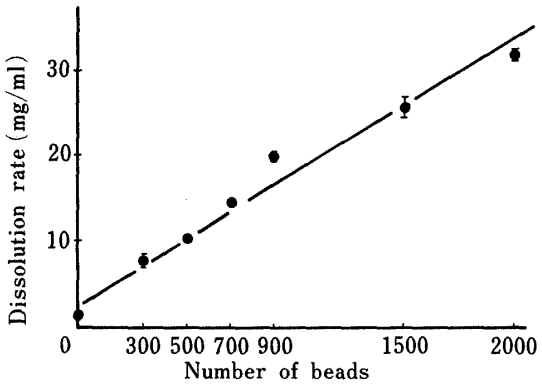

Fig. 4. Relationship between the Number of Beads and the Dissolution Rate

Each point represents the mean ± S.E. of 3 determinations.

beads, in other words, the dissolution rate of drug was determined by the surface area of beads.

The number of beads used in the following experiments was set at 900, because this number of beads was experimentally convenient.

Effect of Rotation Speed of the Paddle

Figure 5 shows the effect of rotation speed of the paddle on the dissolution rate of the drug. At each rotation speed, a linear dissolution curve was obtained, and the dissolution rate was calculated from the slope. Figure 6 shows the relationship between the paddle rotation speed and the dissolution rate. The dissolution rate from preparation b increased with increasing rotation speed in the range of 50 rpm to 100 rpm. However, the dissolution rate slightly decreased with increasing rotation speed above 100 rpm. These results may be

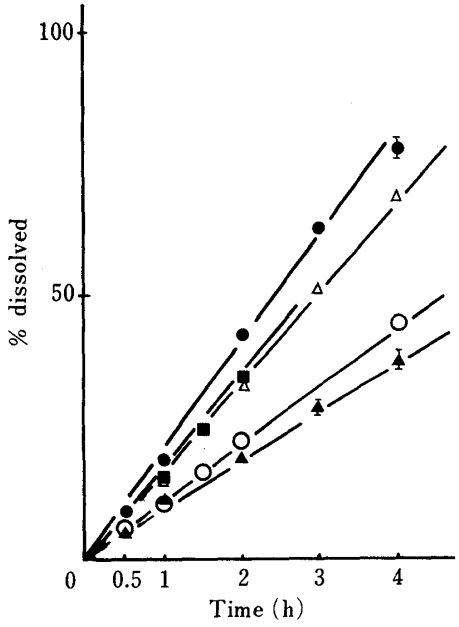

Fig. 5. Effect of the Rotation Speed on the Dissolution of *d*-α-Tocopherol from Preparation b in the Bead Method

Rotation speed (rpm): (▲) 50, (○) 75, (●) 100, (■) 125, (△) 150.
Each point represents the mean±S.E. of three determinations. Conditions of dissolution test: dissolution test medium, 1000 ml; number of beads and diameter, 900 and 4.8 mm.

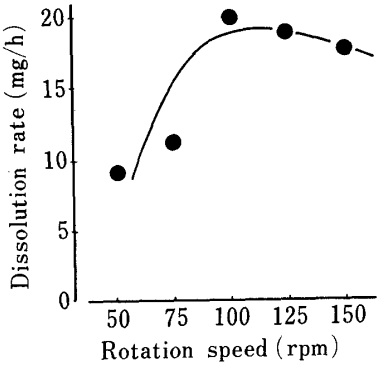

Fig. 6. Relation between the Dissolution Rate from Preparation b and the Rotation Speed of the Paddle

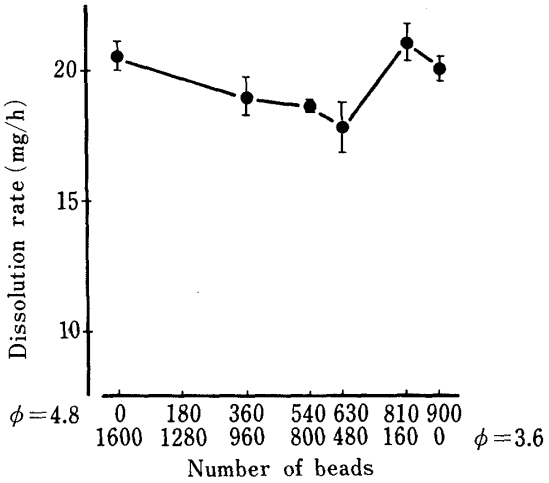

Fig. 7. Dissolution Rate of *d*-α-Tocopherol from Preparation b with Various Combinations of Two Different Diameter Beads at a Constant Total Surface Area of Beads

Each point represents the mean±S.E. of 3—5 determinations. Conditions of dissolution test: dissolution test medium, 1000 ml; rotation speed of paddle, 100 rpm.

explained as follows: in the range of 50 rpm to 100 rpm, the stirring efficiency is enhanced with increase of the speed, but above 100 rpm, the dissolution test medium begins to rotate with the beads and paddle. In addition, the up-and-down movement of beads, which occurs owing to the buoyancy of the beads and the downward force produced by rotation of the assistant wing, decreases with increasing rotation speed. Consequently, the stirring efficiency was not enhanced by the beads and assistant wing at speeds above 100 rpm. These results indicate that there is an optimum rotation speed of the paddle, and in this experimental system, that speed seemed to be 100 rpm.

Mechanism of the Enhancement of Dissolution in the Bead Method

The dissolution rate, as already described, depended on the number of beads, and the

movement of beads in the dissolution test medium also affected the dissolution rate. From these results, the enhancement of dissolution in the bead method is assumed to be due to increased surface area of drug as a result of the addition of beads, or physical effects such as the collision between beads, or both.

Figure 7 shows the results of dissolution tests carried out using two kinds of beads and changing the numbers of beads while keeping the total surface area of beads constant. The dissolution rate was not much changed, and was not much affected by the various combinations of beads. This result indicates that the effect of increased surface area on the increase of dissolution rate is the largest. However, some variation was observed, suggesting the involvement of some other factor in the enhancement of dissolution. Accordingly, a more delailed study seems to be required.

References and Notes

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