# Development of a New Disintegration Method for Orally Disintegrating Tablets

Ryo KAKUTANI,* Hiroyuki MURO, and Tadashi MAKINO

*Novel Pharmaceutical Labs, Kyoto Pharmaceutical Industries, Ltd.; 38 Nishinokyo Tsukinowa-cho, Nakagyo-ku, Kyoto 604–8444, Japan.* Received November 16, 2009; accepted April 27, 2010; published online May 6, 2010

**Recently, the focus has been on the importance of assessing the oral disintegrative properties of orally disintegrating tablets (ODTs). In particular, in the development stages and the quality control field of ODT products, a physical assessment method which easily measures oral disintegrative properties is desired. For this reason, we developed a new disintegration test method (Kyoto-model disintegration method or KYO method), which is useful to predict the oral disintegrative properties of an ODT easily, and examined the availability of the method. In the KYO method, ODT samples were classified in terms of their water permeability, and a moderate water volume was decided. Subsequently, the disintegrative properties were assessed with the newly proposed method. For 25 commercial prescription ODTs used as samples, a good correlation was shown between the results of a human sensory test by five healthy male volunteers and the results using the KYO method. Furthermore, the KYO method could evaluate time-dependent changes in ODT samples. On the other hand, no correlation was observed between the Japanese Pharmacopeia disintegration test and the human sensory test. These results suggested that the KYO method reflected the disintegration nature of the ODTs in the oral cavity, and could easily be applied to development stages and the quality control field of ODT products.**

**Key words** orally disintegrating tablet; new disintegration method; disintegration test

In recent years, orally disintegrating tablets (ODTs) have become widely used among the elderly and children who have difficulty taking medicines because of their poor swallowing capability. As of May 2009, 19 active pharmaceutical ingredients have been formulated into ODTs, and 121 ODTs, including generic drugs and content-different drugs, have been commercialized. The convenience of ODTs is also recognized by patients and medical staff, and ODT products will increase in the future.[1—3] The more popular ODTs become, the more important it is to assess their oral disintegrative properties. In particular, in development stages and the quality control field of ODT products, an assessment method which easily measures oral disintegrative properties is desirable.

Focusing on a tri-regional Pharmacopeia, that is the Japanese Pharmacopeia (JP), United States Pharmacopeia (USP) and European Pharmacopeia (EP), the EP has categorized orodispersible tablets as tablets which disintegrate in less than 3 min using a conventional test.[4] More recently, in the USP, ODTs are considered as solid oral preparations that disintegrate rapidly in the oral cavity, with an *in-vitro* disintegration time of approximately 30 s or less, when based on the USP disintegration test method[5]; however, the JP has not yet defined a disintegration test for ODTs.

Although some disintegration devices for ODTs are marketed,[6—8] they require complicated electrical equipment; therefore, we developed a simple disintegration test method (Kyoto-model disintegration method or KYO method), which can predict the oral disintegrating properties of ODTs. We also measured the oral disintegration properties of 25 commercial prescription ODTs, and examined the viability of the method.

## Experimental

**Materials** The various commercial ODTs used in this study are shown in Table 1. ODTs were selected and purchased from as many manufacturers as possible. The diameter and thickness of the tablets were 7.0 to 11.5 mm and 2.4 to 4.8 mm, respectively.

**Measurement of Disintegration Time in the Human Sensory Test** The disintegration time of ODT samples was measured in five healthy male volunteers in their 20 to 50 s. The disintegration test in the oral cavity was assessed according to the method described by Ogata *et al.*[9] The volunteers were informed of the protocol and purpose of the study. All volunteers were asked to rinse their oral cavity with a little water prior to the test. Each volunteer was asked to place one tablet on the tongue and close the mouth, and a stopwatch was started immediately. Subsequently, the tongue was moved gently, pressing against the upper jaw. The end point of disintegration in the human sensory test was defined as the time when the tablet placed on the tongue had disintegrated without leaving any lumps. All the volunteers were instructed to rinse their mouth after completion of the test. This study was

Table 1. ODT Samples Used in this Study

| Sample No. | Supplier | Remarks |
|---|---|---|
| 1 | A | WOWTAB-DRY |
| 2 | B | |
| 3 | C | |
| 4 | D | |
| 5 | E | EXLUB/SOLBLET |
| 6 | F | |
| 7 | G | |
| 8 | H | PEATAB® |
| 9 | I | |
| 10 | J | |
| 11 | K | |
| 12 | L | |
| 13 | M | |
| 14 | F | |
| 15 | K | |
| 16 | L | |
| 17 | M | Containing enteric coating granules |
| 18 | K | Containing enteric coating granules |
| 19 | N | |
| 20 | O | EXLUB/SOLBLET |
| 21 | P | OL-Melt |
| 22 | Q | |
| 23 | R | Satab® |
| 24 | H | SUITAB® |
| 25 | S | |

* To whom correspondence should be addressed. e-mail: kakutani@kyoto-pharm.co.jp

performed in accordance with the regulations of the Declaration of Helsinki. The data show the mean of three determinations.

**JP Disintegration Test** The disintegration time in the JP disintegration test was measured visually using a stopwatch without a disk. The disintegration medium was 900 ml purified water at 37 °C. The rotation speed was 30 rpm. The data show the mean of six determinations.

**New Disintegration Method. The Kyoto-Model Disintegration Method** In the Kyoto-model disintegration method (or the KYO method), ODT samples were classified in terms of water permeability and a suitable water volume was decided. Subsequently, the disintegrative properties were evaluated by a newly proposed method with two weights placed on the upper surface of the tablet.

Measurement of the Water Permeability of an ODT Sample: One piece of filter paper (21 mm in diameter) was placed in a flat-bottomed test tube (22 mm in internal diameter) set at 37 °C and an ODT sample was placed in the center of the filter paper. Then, 0.5 ml purified water at 37 °C was added to the test tube without directly splashing the tablet. The water permeation time of an ODT was measured as the time when water covered the upper surface of the tablet completely. The water permeation time was defined as the water permeability of an ODT.

Measurement of the Disintegrative Properties of an ODT Sample: One piece of filter paper (21 mm in diameter) was placed in a flat-bottomed test tube (22 mm in internal diameter) set at 37 °C and an ODT sample was placed in the center of the filter paper. The measuring instrument shown in Fig. 1 was placed on the upper surface of the tablet. The measuring instrument imposes a double weight on the tablet, a weight in the center of the upper surface of the tablet and on the marginal portion of the upper surface of the tablet, dubbed "inner weight" and "outer weight," respectively. The outer weight, which had four wedge-shaped boards, as shown in Fig. 2 left, was placed as shown in Fig. 2 right. Thereafter, 0.5 ml or 5 ml purified water were added to the test tube. The volume of water was decided by the water permeation time of each ODT sample. If the water permeation time was less than 60 s, 0.5 ml purified water were added, and if the water permeation time was more than 60 s, 5 ml purified water were added. The completion of disintegration of an ODT sample was defined as the time when the tips of both outer and inner weights made contact with the filter paper. The data are the mean of six determinations.

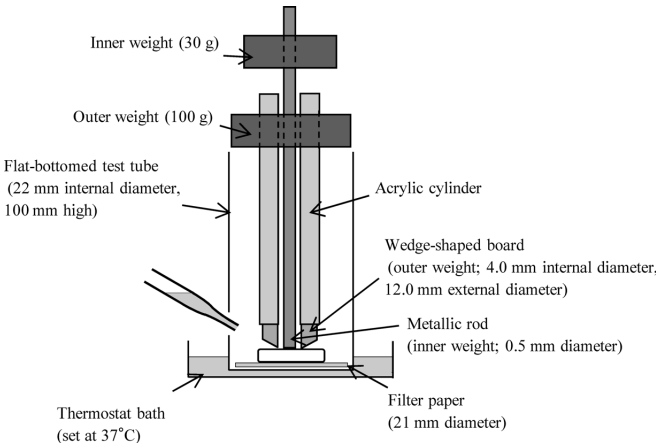


Fig. 1. Instrument for the KYO Method

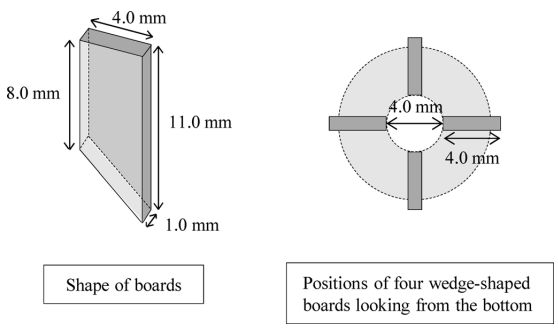


Fig. 2. Shape and Position of Boards

**Measurement of Disintegration Time Using the Single Weight Method** To assess the effect of the outer weight, we assessed the disintegration time of an ODT sample using the single weight method, that is, using the inner weight only. Eighteen ODT samples selected randomly from Table 1 were tested.

One piece of filter paper (21 mm in diameter) was placed in a flat-bottomed test tube (22 mm internal diameter) set at 37 °C and an ODT sample was placed in the center of the filter paper. A metallic rod (0.5 mm in diameter, weight 30 g) was placed at the center of the upper surface of the tablet. Thereafter, 0.5 ml or 5 ml purified water were added, similarly to the KYO method. The completion of disintegration of an ODT sample was defined as the time when the tip of the metallic rod made contact with the filter paper. The data show the mean of six determinations.

**Measurement of Disintegration Time of ODT Samples Stored under Stress Conditions** Eighteen ODT samples selected randomly from Table 1 were stored under stress conditions of 40 °C/75% RH for 1 week, and the disintegration time was measured using the KYO method. The disintegration times of stored samples were compared with those of the initial samples. The data are the mean of six determinations.

## Results

**Disintegration Time of ODT Samples in the JP Disintegration Test and Human Sensory Test** As shown in Table 2 and Fig. 3, there was no relationship between the disintegration times determined by the JP disintegration test and those of the human sensory test ($R^2=0.04$, $r=0.21$), and in the majority of ODT samples, the disintegration times in the JP disintegration test differed from those in the human sensory test. These results suggested that it was very difficult to predict the oral disintegration time using the JP disintegration test.

**Disintegration Time of ODT Samples Using the KYO Method and Human Sensory Test** The water permeation time of 25 ODT samples was classified as less than 60 s or more than 60 s; therefore, if the water permeation time was

Table 2. Disintegration Time of ODT Samples in the JP Disintegration Test and Human Sensory Test, and the Difference in These Disintegration Times

| Sample No. | Disintegration time (s) | | Difference in these disintegration times (s) |
|---|---|---|---|
| | JP disintegration test | Human sensory test | |
| 1 | 48 | 17 | 31 |
| 2 | 10 | 20 | −10 |
| 3 | 26 | 36 | −10 |
| 4 | 21 | 44 | −23 |
| 5 | 11 | 14 | −3 |
| 6 | 45 | 26 | 19 |
| 7 | 18 | 14 | 4 |
| 8 | 31 | 30 | 1 |
| 9 | 29 | 32 | −3 |
| 10 | 31 | 29 | 2 |
| 11 | 41 | 46 | −5 |
| 12 | 16 | 24 | −8 |
| 13 | 36 | 29 | 7 |
| 14 | 33 | 18 | 15 |
| 15 | 21 | 23 | −2 |
| 16 | 20 | 27 | −7 |
| 17 | 28 | 36 | −8 |
| 18 | 18 | 30 | −12 |
| 19 | 11 | 30 | −19 |
| 20 | 20 | 16 | 4 |
| 21 | 48 | 25 | 23 |
| 22 | 47 | 27 | 20 |
| 23 | 26 | 20 | 6 |
| 24 | 29 | 23 | 6 |
| 25 | 16 | 14 | 2 |

less than 60 s, 0.5 ml water were added, and if the water permeation time was more than 60 s, 5 ml water were added. With regard to the tested ODT samples, the disintegration time in the KYO method was more similar to the human sensory test than in the JP disintegration test, and a good correlation was observed between the KYO method and the human sensory test, as shown in Table 3 and Fig. 4 ($R^2$= 0.72, $r$=0.85). On the other hand, as for an ODT made with the Satab® manufacturing process, such as sample No. 23, the disintegration time using the KYO method was much shorter than in the human sensory test, with a great difference in times; however, the oral dissolution of this ODT is comparatively good. Similarly, regarding ODTs such as sample No. 3 and No. 11, the disintegration time using the KYO method was much longer than in the human sensory test, and the oral dissolution was poor. These results suggested that the KYO method can at least assess the disintegrative properties of an ODT in the oral cavity.

**Disintegration Time of ODT Samples Using the Single Weight Method** The disintegration times of 18 ODT samples using the single weight method were generally shorter than when using the KYO method, as shown in Table 4 and

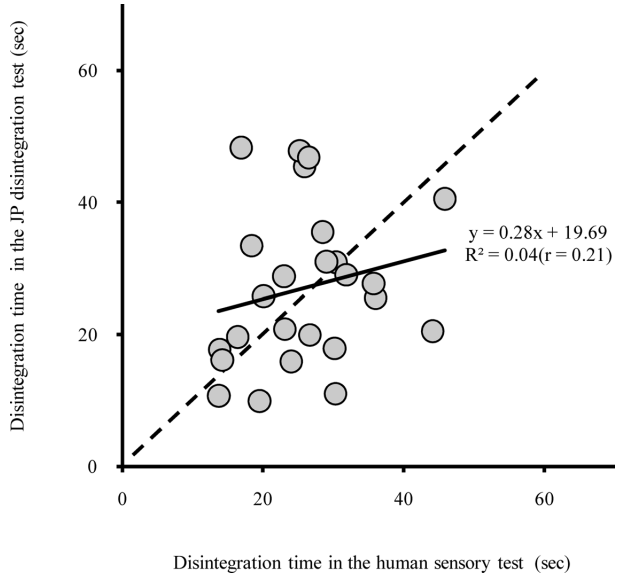


Fig. 3. Relationship between Disintegration Time in the Human Sensory Test and JP Disintegration Test

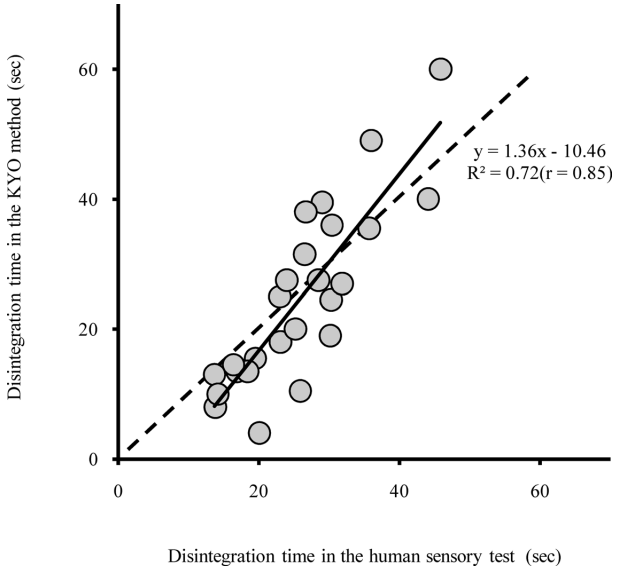


Fig. 4. Relationship between Disintegration Time in the Human Sensory Test and KYO Method

Table 3. Disintegration Time of ODT Samples with the KYO Method and Human Sensory Test, and the Difference in These Disintegration Times

| Sample No. | Water permeation time (s) | Water volume (ml) | Disintegration time (s) | | Difference in these disintegration times (s) |
|---|---|---|---|---|---|
| | | | KYO method | Human sensory test | |
| 1 | 29 | 0.5 | 14 | 17 | −3 |
| 2 | 12 | 0.5 | 16 | 20 | −4 |
| 3 | 27 | 0.5 | 49 | 36 | 13 |
| 4 | 24 | 0.5 | 40 | 44 | −4 |
| 5 | 13 | 0.5 | 13 | 14 | −1 |
| 6 | 32 | 0.5 | 11 | 26 | −15 |
| 7 | 8 | 0.5 | 8 | 14 | −6 |
| 8 | 39 | 0.5 | 36 | 30 | 6 |
| 9 | 91 | 5 | 27 | 32 | −5 |
| 10 | 38 | 0.5 | 40 | 29 | 11 |
| 11 | 37 | 0.5 | 60 | 46 | 14 |
| 12 | 21 | 0.5 | 28 | 24 | 4 |
| 13 | 113 | 5 | 28 | 29 | −1 |
| 14 | 18 | 0.5 | 14 | 18 | −4 |
| 15 | 18 | 0.5 | 18 | 23 | −5 |
| 16 | 8 | 0.5 | 38 | 27 | 11 |
| 17 | 66 | 5 | 36 | 36 | 0 |
| 18 | 120< | 5 | 19 | 30 | −11 |
| 19 | 11 | 0.5 | 25 | 30 | −5 |
| 20 | 14 | 0.5 | 15 | 16 | −1 |
| 21 | 69 | 5 | 20 | 25 | −5 |
| 22 | 68 | 5 | 32 | 27 | 5 |
| 23 | 5 | 0.5 | 4 | 20 | −16 |
| 24 | 23 | 0.5 | 25 | 23 | 2 |
| 25 | 9 | 0.5 | 10 | 14 | −4 |

Fig. 5, and a good correlation was observed between the single weight method and the human sensory test ($R^2$=0.50, $r$=0.71). The disintegration times of samples were considerably different; therefore, we assumed that the outer weight in the KYO method had some critical role leading to a better correlation between the KYO method and the human sensory test.

**Applicability of the KYO Method in Stored ODT Samples** In 18 stored ODT samples, a good correlation was observed in the disintegration time between the KYO method and human sensory test, as shown in Table 5 and Fig. 6 ($R^2$=0.58, $r$=0.76). When the disintegration times of the initial and stored ODT samples were compared, as shown in Fig. 7, there was a good correlation in the difference between these disintegration times ($R^2$=0.75, $r$=0.86), and the slope was close to 1; therefore, it is suggested that the KYO method is also applicable to predict the oral disintegration time of time-dependent changed ODTs.

Table 4. Disintegration Time of ODT Samples with the Single Weight Method and the Difference in Disintegration Times between the Single Weight Method and KYO Method

| Sample No. | Water volume (ml) | Disintegration time with the single weight method (s) | Difference in these disintegration times (s) |
|---|---|---|---|
| 1 | 0.5 | 14 | 0 |
| 2 | 0.5 | 10 | −6 |
| 3 | 0.5 | 29 | −20 |
| 4 | 0.5 | 27 | −13 |
| 5 | 0.5 | 10 | −3 |
| 6 | 0.5 | 8 | −3 |
| 8 | 0.5 | 31 | −8 |
| 13 | 5 | 20 | 0 |
| 14 | 0.5 | 14 | −5 |
| 15 | 0.5 | 17 | −8 |
| 17 | 5 | 23 | −8 |
| 19 | 0.5 | 10 | −7 |
| 20 | 0.5 | 12 | −14 |
| 21 | 5 | 21 | 0 |
| 22 | 5 | 25 | −1 |
| 23 | 0.5 | 4 | −18 |
| 24 | 0.5 | 21 | −13 |
| 25 | 0.5 | 8 | −4 |

## Discussion

We assumed that the mechanism of the oral disintegration of an ODT involved a three-step disintegration process, as shown in Fig. 8; after an ODT is placed in the oral cavity, [1] saliva permeates the surface of the ODT, [2] this permeated region is softened, and [3] the softened portion is destroyed and removed by tongue pressure and friction between the tongue and the upper jaw. Next, saliva again permeates the non-disintegrated region of the ODT. After following these steps several times, the ODT disintegrates completely. With the KYO method, a double weight, outer and inner weights,

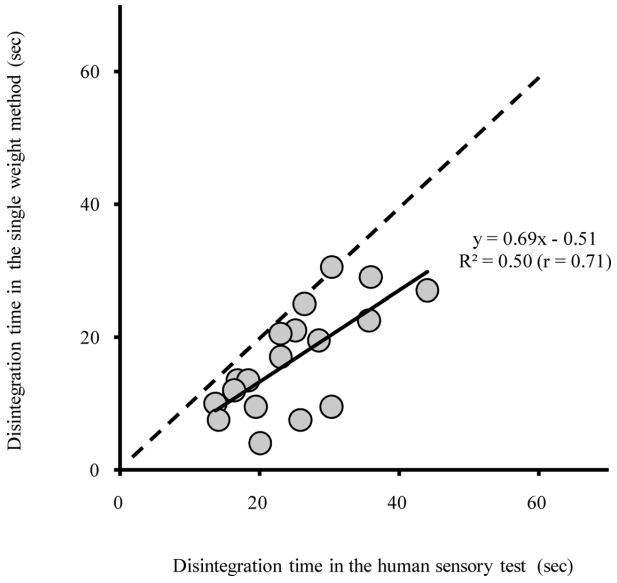


Fig. 5. Relationship between Disintegration Time with Human Sensory Test and Single Weight Method

Table 5. Disintegration Times of ODT Samples before and after Time-Dependent Changes with the KYO Method and Human Sensory Test, and the Difference in These Disintegration Times

| Sample No. | Disintegration time in the KYO method (s) | | | Disintegration time in human sensory test (s) | | |
|---|---|---|---|---|---|---|
| | Before | After | Difference in these disintegration times | Before | After | Differences in these disintegration times |
| 1 | 14 | 11 | −3 | 17 | 10 | −7 |
| 2 | 16 | 18 | 2 | 19 | 16 | −3 |
| 3 | 49 | 31 | −18 | 36 | 24 | −12 |
| 4 | 40 | 12 | −28 | 44 | 18 | −26 |
| 5 | 13 | 13 | 0 | 14 | 14 | 0 |
| 6 | 11 | 5 | −6 | 26 | 14 | −12 |
| 8 | 36 | 34 | −2 | 30 | 29 | −1 |
| 13 | 28 | 29 | 1 | 29 | 31 | 2 |
| 14 | 14 | 31 | 17 | 18 | 42 | 24 |
| 15 | 18 | 19 | 1 | 23 | 18 | −5 |
| 17 | 36 | 37 | 1 | 36 | 30 | −6 |
| 19 | 25 | 3 | −22 | 30 | 8 | −22 |
| 20 | 15 | 18 | 3 | 16 | 18 | 2 |
| 21 | 20 | 34 | 14 | 25 | 27 | 2 |
| 22 | 32 | 17 | −15 | 26 | 23 | −3 |
| 23 | 4 | 4 | 0 | 20 | 25 | 5 |
| 24 | 25 | 11 | −14 | 23 | 13 | −10 |
| 25 | 10 | 17 | 7 | 14 | 15 | 1 |

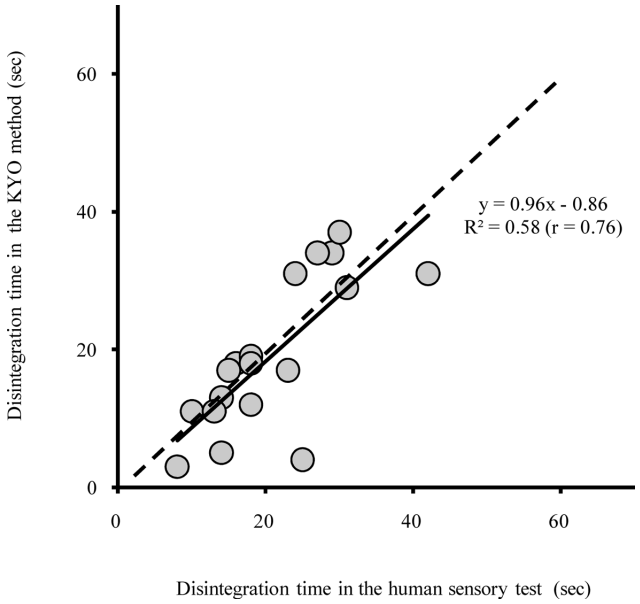


Fig. 6. Relationship between Disintegration with the Human Sensory Test and KYO Method for Time-Dependent Changes in ODT Samples

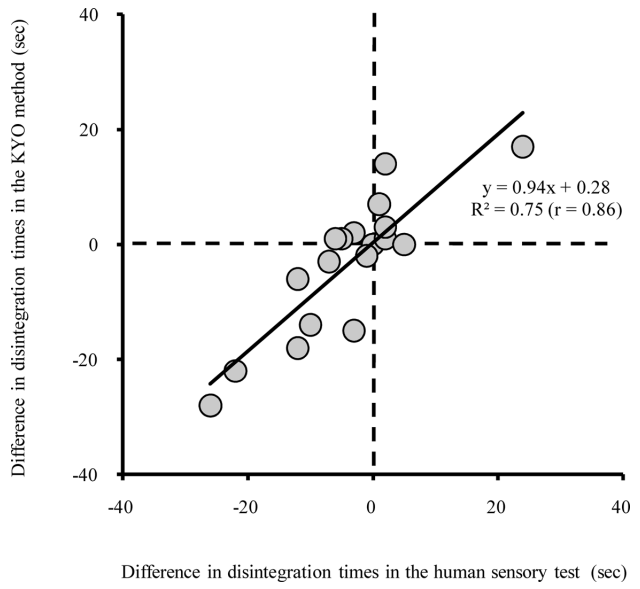


Fig. 7. Difference of Disintegration Times before and after Time-Dependent Changes in ODT Samples

are placed on the upper surface of an ODT sample. We assumed that the double weight of the KYO method would be reflected in the oral disintegration mechanism. As shown in Fig. 9, the disintegration mechanism in the KYO method passes though the following steps: [1] water permeability of an ODT, [2] softening of the permeated region, [3] destruction and removal of the marginal region due to outer weight action, [4] new water permeation of the non-disintegrated region, and [5] disintegration of the central region due to inner weight action. In particular, the KYO method reflects the steps of "destruction and removal of the marginal region" and "saliva permeation of the non-disintegrated region" in the oral cavity. Furthermore, since the disintegration times of 18 ODT samples with the single weight method were generally shorter than with the KYO method, we considered that the outer weight was related to the control of tablet swelling; that is, the control of water permeation into the tablet because of weight on the upper surface.

Before the disintegration time was measured using the KYO method, the samples were classified into two types in accordance with their water permeability to decide an adequate volume of water for each ODT sample. We assumed that the slower the samples disintegrated in the oral cavity, the more saliva volume they required. For this reason, if the water permeation time was less than 60 s, 0.5 ml purified water were added, and if the water permeation time was more than 60 s, 5 ml purified water, which was a sufficient volume for oral disintegration, were added. Furthermore, 60 s was set as the threshold value in the KYO method because all of the water permeation times of the tested ODTs were classified as less than 40 s or more than 60 s.

In the tested ODTs, no relationship was observed between the tablet size and the water penetration or the disintegration times in the JP disintegration test and the KYO method. These results suggested that the water penetration and these disintegration times were related to the formulations and the manufacturing processes of ODTs, not the tablet size.

As for an ODT made using a manufacturing process called Satab®, the disintegration time measured in the KYO method was much shorter than in the human sensory test, and the difference in these measured values was great. We assumed that the difference in the disintegration times resulted from the high hydrophilic property of sodium stearyl fumarate used as a lubricant and the high porosity of the tablet.

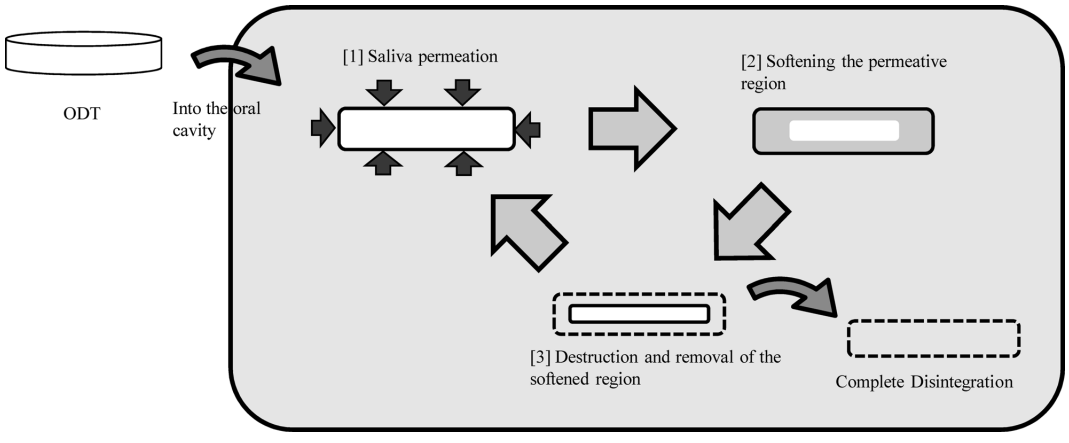


Fig. 8. Disintegration Mechanism of ODTs in the Oral Cavity

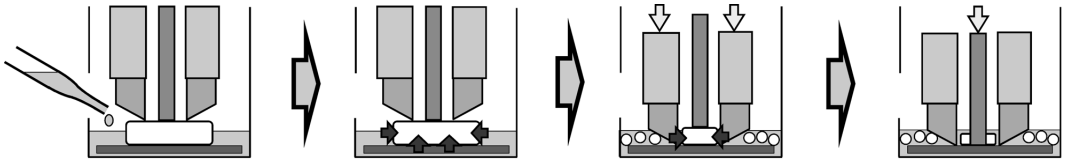


Fig. 9. Disintegration Mechanism of the KYO Method

Based on the disintegration time, the stored ODTs were divided into two groups, a faster disintegration group and a slower disintegration group, compared with their initial values. Stored in warm and humid conditions, ODTs containing high water-absorbing excipients tended to have a faster disintegration nature and ODTs containing heat-melting excipients occasionally had a slower disintegration nature because of changes in their physical properties.

Some disintegration devices for ODTs are on the market and they all require sophisticated electrical equipment. Although the KYO method requires a special measuring instrument, it needs no sophisticated electrical equipment. Furthermore, although the KYO method requires equipment such as a thermostat bath and a pipetter, these are found in all laboratories. Using the KYO method, the disintegration time of most ODT samples was similar to that in the oral cavity, and a good correlation was observed between the two methods.

The marketed devices have not shown much data on the disintegration test for ODTs; therefore, we cannot discuss differences between the new disintegration test and the marketed devices. We consider that the differences will be shown more clearly as the necessity of assessing the disintegration time of ODTs becomes more important in the future.

## Conclusion

Using the KYO method, the disintegration time of most ODT samples was similar to that in the oral cavity, and a good correlation was observed between the two methods.

In this study, we evaluated the oral disintegrative properties of 25 commercial ODT products. According to the results, there was no relationship between the disintegration times determined in the JP disintegration test and a human sensory test. These results suggested that it was very difficult to predict the disintegration time in the oral cavity from measurements in the JP disintegration test. On the other hand, the disintegration time using the KYO method was more similar to the human sensory test, and a good correlation was observed between the two methods. These results also show that the disintegrating mechanism with the KYO method is similar to the mechanism of actual oral disintegration in terms of the action of the double weights and adequate water volume. Moreover, the KYO method was also applicable to predict the oral disintegration time for time-dependent changes of ODTs. In summary, we conclude that the new proposal disintegration method, dubbed the Kyoto model disintegration method (or the KYO method), can easily evaluate the oral disintegrating time of ODT formulations in the development stages and during quality control.[10)]

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