Evaluation of the Disintegration Time of Rapidly Disintegrating Tablets *via* a Novel Method Utilizing a CCD Camera

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Many kinds of rapidly disintegrating or oral disintegrating tablets (RDT) have been developed to improve the ease of tablet administration, especially for elderly and pediatric patients. In these cases, knowledge regarding disintegration behavior appears important with respect to the development of such a novel tablet. Ordinary disintegration testing, such as the Japanese Pharmacopoeia (JP) method, faces limitations with respect to the evaluation of rapid disintegration due to strong agitation. Therefore, we have developed a novel apparatus and method to determine the dissolution of the RDT. The novel device consists of a disintegrating bath and CCD camera interfaced with a personal computer equipped with motion capture and image analysis software. A newly developed RDT containing various types of binder was evaluated with this protocol. In this method, disintegration occurs in a mildly agitated medium, which allows differentiation of minor distinctions among RDTs of different formulations. Simultaneously, we were also able to detect qualitative information, *i.e.*, morphological changes in the tablet during disintegration. This method is useful for the evaluation of the disintegration of RDT during pharmaceutical development, and also for quality control during production.

Key words disintegration test; rapidly disintegrating tablet; CCD camera; oral disintegration

The proportion of society composed of elderly individuals has risen, indicative of increased longevity.[1)] Hence, it is of increasing importance to address the medicinal needs of this segment of the population in terms of conventional dosage forms such as powders, tablets and capsules.[2)] In this regard, to improve the quality of life and treatment compliance of such patients, a fast dissolving oral dosage in the form of rapidly disintegrating tablets (RDT) appears to be a suitable alternative for oral medication, accounting for difficulties associated with swallowing often encountered by this segment of the population.[3,4)]

Upon placement of tablets of this type within the oral cavity, saliva quickly penetrates into the pores, causing rapid tablet disintegration. Thus, disintegration time is an important property of tablets, but it must be evaluated. *In vitro* disintegration time can be tested *via* the Japanese Pharmacopoeia (JP) XIII disintegration test; however, according to the literature, this approach does not appear to be convenient for measuring the disintegration time of RDT.[5—8)]

As an alternative to the apparatus described in JP XIII, we developed a novel approach in order to evaluate the disintegration time of RDT employing a CCD camera. We attempted to predict the *in vivo* disintegration time and to clarify the disintegration mechanism of RDT with this device. For these purposes, three RDT samples were designed with mannitol and different types of binders, including polyvinylpyrrolidone, polyvinylalcohol and hydroxypropylcellulose.

Experimental

Materials D-Mannitol (Mannit P, Towa Chemical Industry Co., Ltd., Tokyo) (particle size of 52 μm in median diameter by the laser scattering method, LA-910, Horiba, Ltd., Kyoto) was utilized. Polyvinylpyrrolidone JP (PVP-K30, ISP Technologies Inc., New Jersey), 88 mol% hydrolyzed polyvinylalcohol (PVA205C, Kuraray Co., Ltd., Tokyo) and hydroxypropylcellulose JP (HPC-L, Nihon Soda Co., Ltd., Tokyo) were employed as binders. Ethanol was of analytical grade of not less than 99.5% (Junsei Chemical Co., Ltd., Tokyo). Other chemicals were of a commercial grade.

Preparation of the Test Tablets Formulations employed in this study are presented in Table 1. Test tablets involved in the evaluation and prediction of oral disintegration were prepared with various binder types and quantities in order to assess the suitability of the CCD-camera method with respect to the examination of *in vivo* disintegration. A schematic diagram of the preparation technique of the test tablets is shown in Fig. 1. D-Mannitol was crushed in a high-speed mixer equipped with 3-l vessel (Mechanomil MM-10, Okada Seiko Co., Ltd., Tokyo). Binder was dissolved in a solvent composed of a 50% (w/w) ethanol solution. The amount of the solvent used was 13% (w/w) to the tablet weight. D-Mannitol was kneaded with the binder solution in order to achieve uniform moisture. Subsequently, the wet powder was compressed by a novel molding tableting system,[9—11)] which consisted of a molding tableting machine and a belt dryer, developed by Eisai Co., Ltd. (Tokyo) and Sankyo Seisakusho Co. (Tokyo). Following drying with the belt dryer, tablets were dried in a tray dryer (DAE-20, Sanwa Kaki Kogyo Co., Ltd., Tokyo) in order to reduce the loss on drying of the tablets below 0.5% (w/w) on a wet weight basis.

Table 1. Formulations of Test Tablets

(w/w%)

Formula No.	1	2	3	4	5	6	7	8	9	10	11	12
Mannitol	99.69	98.31	99.00	99.00	98.50	98.00	97.50	99.50	99.25	99.00	98.75	98.50
PVP K30	0.31	1.69	1.00	—	—	—	—	—	—	—	—	—
HPC-L	—	—	—	1.00	1.50	2.00	2.50	—	—	—	—	—
PVA205C	—	—	—	—	—	—	—	0.50	0.75	1.00	1.25	1.50
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

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Table 2. Tablet Properties and Results for Disintegration Tests

Type of binder	Amount of binder (%(w/w))	Weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (KgF)	Friability (%)	LOD (%)	Ep[a)] (min)	*AUC*[a)] (pixel·sec)	Disintegration time (s)	
										JP	Oral
PVP	0.307	271.9	3.91	9.47	2.74	0.97	0.15	5.51	296400	19.0	4.6
	1	273.9	3.92	9.48	6.36	0.74	0.18	5.85	339496	16.0	7.3
	1.693	275.3	3.91	9.46	9.11	0.54	0.30	6.64	337107	21.3	7.1
HPC-L	1	293.3	4.04	9.47	8.00	1.19	0.06	4.93	249370	13.2	13.8
	1.5	295.4	4.02	9.47	9.93	1.06	0.12	6.70	332327	23.0	27.7
	2	299.8	4.02	9.47	11.44	0.85	0.10	7.90	403443	37.0	44.7
	2.5	296.7	3.97	9.47	10.12	0.84	0.13	7.86	397352	42.3	41.2
PVA	0.5	284.7	4.03	9.47	5.70	1.70	0.11	2.41	101190	7.7	9.1
	0.75	287.1	4.02	9.47	7.75	1.20	0.09	3.15	139703	8.7	10.9
	1	286.9	4.08	9.46	8.62	1.21	0.09	4.09	169453	9.0	11.6
	1.25	287.3	4.07	9.46	10.70	1.07	0.11	5.11	225785	12.0	15.6
	1.5	291.0	4.11	9.44	11.29	0.98	0.12	4.99	230655	14.3	24.5

a) Ep and *AUC* were obtained *via* CCD camera technique.

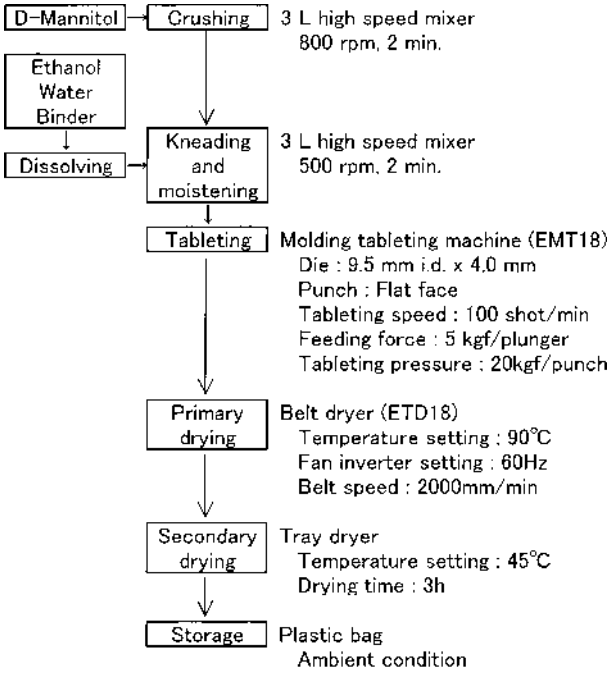

Fig. 1. Preparation Procedure of Rapid Disintegrating Tablet

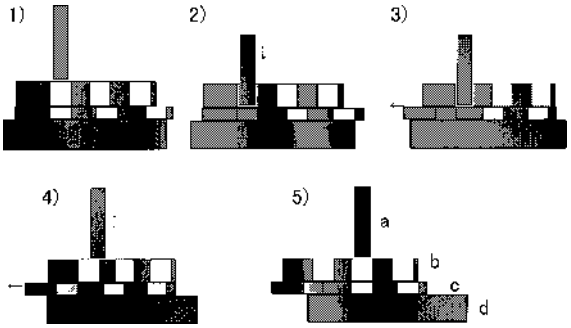

Fig. 2. Schematic Diagram of Filling Mechanism of Wet Powder into Tableting Die in the Main Table

a: Filling plunger, b: subtable, c: main table, d: base. 1) Subtable cavity roughly filled with wet powder overlapping on the die cavity in the main table. 2) Down motion of filling plunger pushes the wet powder into the die cavity. 3) Wet powder is cut within the die cavity by rotation of the main table. 4) Subtable rotates after the filling plunger moves upward. 5) Subtable cavity with wet powder overlaps on the next die cavity.

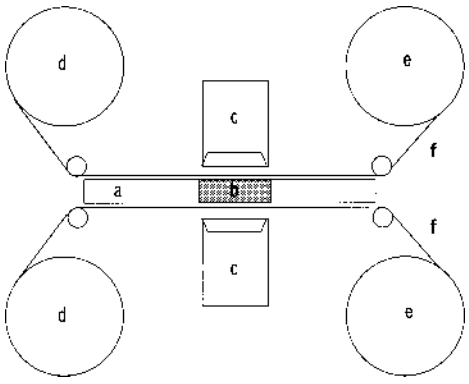

Fig. 3. Film Compression System for Wet Powder Tableting

a) Main table (Set a tableting die). b) Wet powder (Filled by previous technique described in Fig. 2). c) Tableting punch. d) Feeding roll of polymeric film. e) Winding roll of polymeric film. f) Polymeric film.

Typically, tableting of wet powder presents difficulties, which include sticking or adhesion of the powder to the punch, weak mechanical strength, and large weight variation caused by the low flowability of wet powder. The molding tableting machine used in the present study possesses two particular mechanisms which permit wet powder tableting. The first mechanism is a compression powder feeding system, displayed in Fig. 2. Wet powder was fed in two steps as follows: the wet powder introduced into the hopper of the EMT18 was filled roughly to a well of the subtable by oscillation of the feeding blade. Next, the powder in the wells was transferred to a die cavity set in the main table by a plunger at constant pressure. A constant volume of a constant density powder was withdrawn continuously due to this mechanism; as a result, weight variation of the tablets was minimized.

The second mechanism involves a film compression system, described in Fig. 3. Thin polymeric film was placed between the wet powder and the tableting punch, preventing sticking of the moist powder to the punch. In this experiment, polyethylene (0.01 mm in thickness) (Fujimori Kogyo Co., Ltd.) was used as the polymeric film. The belt dryer was utilized for primary drying of wet tablets compressed by the tableting machine immediately after tableting to provide strength with respect to ease of handling.

In the present experiment, a tableting die (9.5 mm i.d.) and a flat face punch were employed. The compression force was 20 kgf/punch (7.06 kgf/cm^2). The tableting speed was 300 tablets per min. The temperature of the belt dryer was set at 90 °C. At the aforementioned tableting speed, the time required to pass the belt dryer was approximately 3 min. The tray dryer was set at 45 °C for 3 h.

Evaluation of Physical Properties of the Tablet The weight, diameter, thickness and hardness of 10 tablets were measured with an electric balance (AE240, Mettler-Toledo AG, Greifensee), digital thickness gauge (Digimatic

indicator, Mitsutoyo Corporation, Tokyo) and hardness tester (KHT-20, Fujiwara Factory Co., Ltd., Tokyo). Hardness of the tablets was determined with diametrical compression. Friability was measured on a Roche type friabilator at 25 rpm for 4 min using 20 tablets. Loss on drying of these tablets was assessed with an infrared moisture determination balance (FD-230, Kett Electric Laboratory, Tokyo) at 85 °C. Disintegration time was measured with a JP disintegration tester (Toyama Sangyo Co., Ltd., Osaka) involving six tablets in a basket equipped with an automatic end point detector (Distopper, Toyama Sangyo Co., Ltd., Osaka). End point determination with the naked eye is not sufficient to accurately evaluate the disintegration time of a rapidly disintegrating tablet due to adherence of the tablet composition to the apparatus.

Oral disintegration time was measured by three volunteers for a series of tablets with different binders. Tablets were placed on the tongue; subsequently, the tongue was gently moved. The time required for the elimination of tips or fragments of the tablets was determined with a stopwatch. This procedure prohibited the swallowing of saliva; additionally, saliva was rinsed from the mouth after each measurement. The average of triplicate measurements represented an individual oral disintegration time.

Operating Structure of Disintegration Test with CCD Camera The CCD camera apparatus is comprised of two distinct sections, a disintegration component and a measurement device. The mode of measurement involves the continuous acquisition of pictures by the CCD camera to record the disintegration time course; these pictures are simultaneously transferred to the computer and stored. The key point of this apparatus is to combine the detailed pictures obtained by the CCD camera and the calculation capabilities of the computer.

The disintegration apparatus consists of a plastic cell partitioned into two parts: one compment is comprised of an inner tank containing the stirring bar, the grid fabricated from stainless-steel and the disintegration medium (distilled water, 200 ml, 37±2 °C); the second component is an outer tank, which functions as a water bath heated at 37±1 °C (Fig. 4a) *via* circulation of thermostated water. The grid is constructed of three hollow areas equidistant from the center. These hollow points represent the position of the tablets, and a support is added for each tablet to avoid movement during the disintegration test (Fig. 4b).

The measurement apparatus consists of a CCD camera (VR-KT75, auto focus F=4, 5—36 mm, ϕ=37 mm, Sharp Co., Ltd., Tokyo) and a computer with Windows98 OS. The CCD camera is positioned such that the top surface of the three tablets can be seen on the camera's screen.

Results and Discussions

Principles of the CCD Camera Apparatus RDT should disintegrate rapidly upon placement in the mouth, yet possess sufficient structural integrity to withstand handling without substantial breakage. Thus, tablet properties such as hardness, porosity and friability are closely linked to causing rapid tablet disintegration.

Disintegration time is an important tablet property. It can be evaluated *in vivo*; the disintegration test in the oral cavity is briefly described in the literature.[5—8] The results from this type of test typically reveal unsatisfactory reproducibility. This is truer in the case of the RDT than ordinary tablets, whereas the disintegration time of RDT is usually less than one minute and differs only by a few seconds in comparison with different formulations. Although oral test results are not completely reliable, it is the only method by which to evaluate *in vivo* disintegration time. Furthermore, the *in vivo* dissolution test is characterized by intrinsic limitations from the perspective of ethics and the safety of the volunteers.

The typical approach by which to measure *in vitro* disintegration time involves utility of the JP XIII disintegration test apparatus. This method does not appear to afford convenience, as the RDT disintegration time is less than one minute; moreover, detection of the endpoint is accomplished by visual observation. Bi *et al.* proposed a modified dissolution apparatus based on the JP technique in which a gentle water current is produced in order to delay disintegration time.[8] Thus, faced with increased interest regarding RDT and the difficulty associated with evaluating the disintegration time of these tablets, the development of a method to improve the reliability of *in vitro* disintegration is necessary. Utility of a CCD camera is a component of this novel apparatus.

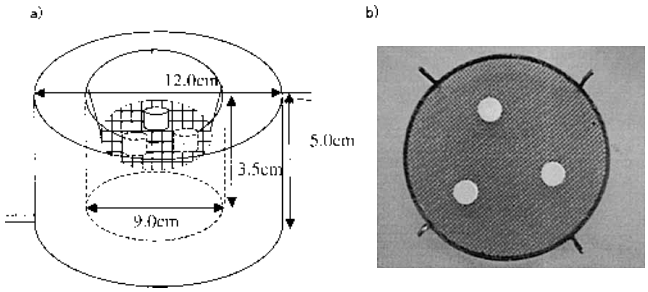

Fig. 4. Plastic Disintegration Cell (a) and Tablet Support Grid with Three RDT (b)

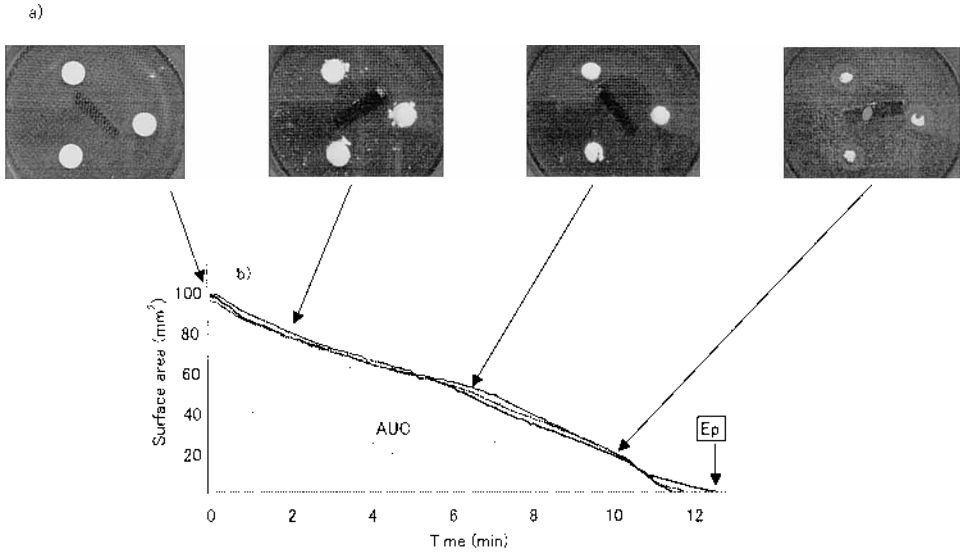

Fig. 5. Example of Photographs Obtained by the CCD Camera (a) and Decrease of the Surface Area of the RDT as a Function of Time (b)

In fact, the pharmacopoeia method permits evaluation of the disintegration time; however, no additional information can be extracted. Of course, it is possible to evaluate the tendency of the disintegration time course based on the examination during testing. However, these evaluations are not sufficiently objective. The observations described above are qualitative, affording no possibility of determination of quantitative parameters other than the disintegration time.

The CCD camera method permits documentation of the disintegration time course with pictures obtained sequentially with the CCD camera (Fig. 5a). After testing the desired number of tablets, information extracted from the pictures can be extensively analyzed. The computer, for example, enables calculation of the surface area of each tablet at any time point, as well as the design of graphs similar to that displayed in Fig. 5b. Figure 5b shows a decrease in the tablet surface as a function of time. Disintegration time (end point, Ep) and the area under the curve (*AUC*) can be calculated from these graphs as quantitative parameters that can be correlated to oral disintegration time. Surface area is determined on the basis of tablet pictures; consequently, results depend on the direction and focal length of the camera relative to the tablet. The distance was constant throughout this study; moreover, the surface area represents the top surface of the tablets in arbitrary pixel units.

The disintegration time course can be analyzed based on graphic data; furthermore, important steps within RDT disintegration can be established. Figure 6 depicts a typical example demonstrating the decrease in the RDT surface as a function of time. A peak observed at 2.5 min indicates decomposition of the tablet into several pieces. Several tablets exhibited a completely straight decrease in surface area; several tablets displayed a more complicated shape. Understanding the disintegration mechanism remains complex; however, several general characteristics of the disintegration phenomena can be deduced with this powerful tool.

The disadvantage of the CCD camera method involves difficulty associated with the application of mechanical stress to test tablets. Thus, the time required for a single test is several minutes, which is greater than that for *in vivo* disintegration time. To decrease disintegration testing time, it is necessary to apply mechanical stress to the tablets.

First, the apparatus was tested under various conditions in order to determine the consequences with respect to operating conditions and to determine the robustness of the method. For these purposes, three parameters were selected: the opening mesh size of the grid, the speed of agitation and the size of the stirring bar. Figure 7 illustrates the relationship between disintegration time and each operating condition. Each figure reveals a linear decrease in the disintegration time with an increase in each operating condition; moreover, the multiple coefficient of correlation values, r^2, are sufficiently large. Interestingly, these results suggest that any operating condition can be selected within the range of each condition tested. Based on the above, 1.0-mm mesh size, 200-rpm-agitation and a 3-cm stirring bar were chosen for the remainder of the present investigation.

Relation between Disintegration Parameters Twelve tablet samples containing PVP, HPC-L and PVA binders were tested *in vivo* and *in vitro* using the Pharmacopoeia (with Distopper) and CCD camera methods, respectively. With the CCD camera technique, two parameters were selected in relation to the disintegration phenomena, *i.e.*, the Ep and the *AUC*. *AUC* is calculated from the disintegration curves, as previously explained in the operating structure section. Figure 8 demonstrates the relationship between these two parameters, *AUC* and Ep. A positive linear correlation was observed, characterized by a large correlation coefficient ($r^2=0.9595$). Thus, these two parameters are closely linked; additionally, they function with respect to the disintegration phenomena in an identical manner. From this linear relation, it appears obvious that Ep and *AUC* primarily reflect a slope of the disintegration curve. In fact, rapid disintegration is equivalent to a large slope on the disintegration curve, which results in small values of Ep and *AUC*.

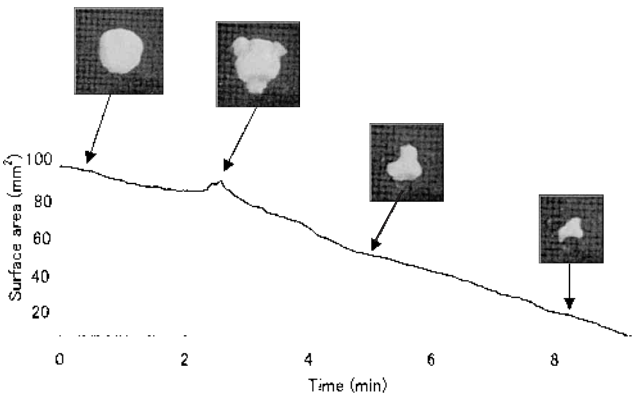

Fig. 6. Decrease of the Surface Area of One Tablet as a Function of Time, and Associated Pictures

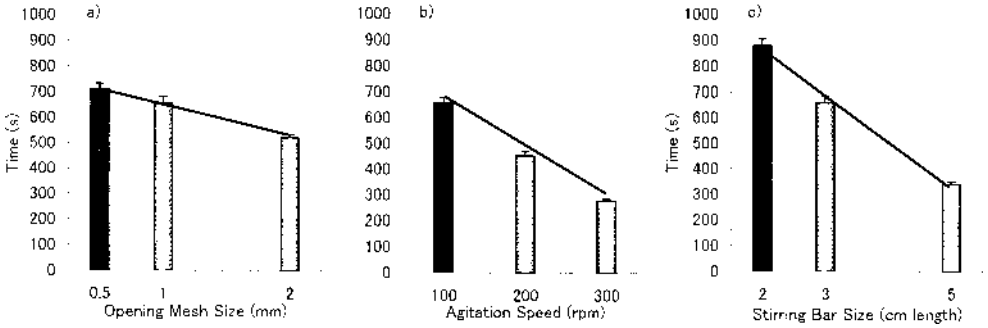

Fig. 7. Relationship between Disintegration Time and Operating Conditions

a) Opening mesh size, $r^2=0.9969$. b) Agitation speed, $r^2=0.9408$. c) Size of stirring bar, $r^2=0.9923$.

Figure 9 illustrates the relationship between oral disintegration time and Ep, *AUC* and JP disintegration time (JP DT). The three sample types with differing binders are marked within the same graph, and the linear equation is calculated for all plots (shown as a dotted line). Each parameter displays a positive correlation with oral disintegration time; however, the correlation coefficients (r^2) are superior in the cases involving JP DT and Ep relative to *AUC*. These r^2 values and standard errors of regression (in parentheses) are 0.6086 (5.2100), 0.5168 (5.7890) and 0.3759 (6.5789) for JP DT, Ep and *AUC*, respectively. None of these values is markedly greater relative to the other; moreover, these values are not large, which underscores the difficulty associated with simulation of the *in vivo* disintegration mechanism. However, both of these parameters can partly explain the *in vivo* disintegration phenomena. It would be interesting to relate the rate of disintegration to oral disintegration time based on the demonstration that Ep and *AUC* are functions of this rate. Several curves are linear; additionally, several curves represent a more complicated shape, the utility of which is impossible.

Equations are calculated for each binder sample, shown as solid lines, rather than for all plots, shown as dotted lines in Fig. 9. In terms of correlation coefficient overall data, Fig. 9c (JP DT) appears to offer the best result. However, Figs. 9a (Ep) and 9b (*AUC*) indicate that the solid lines exhibit a nearly parallel relation. This observation is not identical to the case involving the solid lines in Fig. 9c. This finding suggests that results obtained from the CCD camera method may better individually correlate with oral disintegration time with respect to each binder. On the other hand, parameters of the JP DT could better correlate with the oral disintegration time of RDT, irrespective of binder type. However, in the case of predicting the *in vivo* disintegration of tablets containing different binders, the possibility of enormous error occurs in the JP method, especially in the region of approximately 30 s or higher, during *in vivo* disintegration.

Furthermore, if attention is focused on the tablet containing PVA, oral DT ranged from 11.6 to 29.9 s, which corresponded to the JP DT range of 7.7 to 14.3 s; additionally, this finding was in contrast with the Ep range of 2.4 to 5.1 min. In this case, the range of JP DT was only a few seconds; moreover, it appears difficult to discern differences in the *in vivo* disintegration of the tablet containing PVA. We can conclude that the CCD camera method is a suitable alternative relative to the ordinary testing approach in terms of prediction and estimation of RDT disintegration.

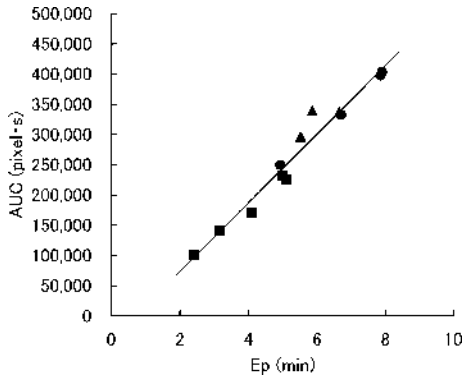

Fig. 8. Relationship between the Area under the Curve (*AUC*) and the Disintegration End Point (Ep)

r^2=0.9595. Tablets comprised of PVP (▲), HPC-L (●) and PVA (■) (n=6).

Conclusion

In order to predict the oral disintegration time of the RDT *via in vitro* methodology, a novel apparatus was developed utilizing a CCD camera. This study demonstrated the ability of this apparatus to assess and quantify several parameters in relation to disintegration time. The oral disintegration mechanism is complex; moreover, the difficulty was underscored with respect to simulation of the oral disintegration phenomena *via* an *in vitro* technique; however, the CCD camera method can partially explain and predict oral disintegration. Hence, the relationship between oral disintegration time and Ep correlates positively for each type of binder. Consequently, this method should be viewed as a universal approach regarding evaluation of the disintegration time of any RDT. This novel apparatus is a prototype and should be improved. Nevertheless, its contribution in terms of prediction of *in vivo* disintegration time is worthy of consideration.

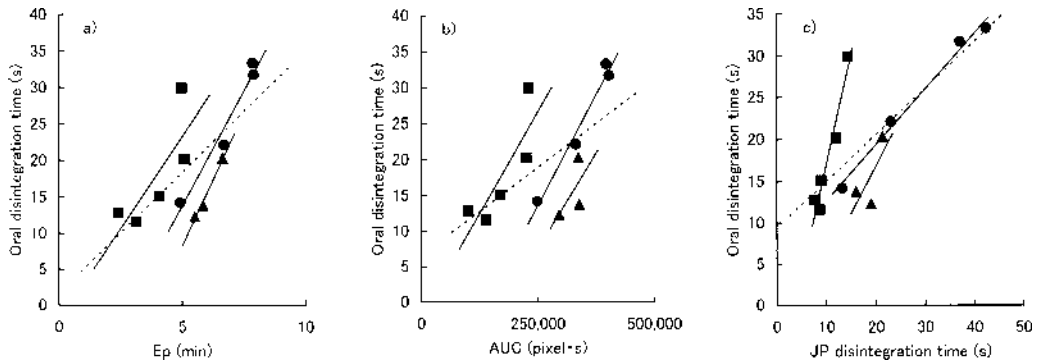

Fig. 9. Relationship between Oral Disintegration Time and the Ep, *AUC* and JP Disintegration Time

Binders for the tablets tested were PVP (▲), HPC-L (●) and PVA (■). Dotted line shows linear regression for overall data. Solid line depicts linear regression for each of the binders. a) CCD Ep and the oral disintegration time. Overall, r^2=0.5168 (5.7890); ▲, r^2=0.9856 (0.7218); ●, r^2=0.9631 (2.0968); ■, r^2=0.6286 (5.5244). b) *AUC* and the oral disintegration time. Overall, r^2=0.3759 (6.5789); ▲, r^2=0.3678 (4.7819); ●, r^2=0.9741 (1.7573); ■, r^2=0.7092 (4.6476). c) JP disintegration time and the oral disintegration time. Overall, r^2=0.6086 (5.2100); ▲, r^2=0.5121 (4.2009); ●, r^2=0.9882 (1.1868); ■, r^2=0.9356 (2.1876). Standard errors of regression are represented in parentheses.

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