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A comparative study of disintegration actions of various disintegrants using Kohonen's self-organizing maps

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ABSTRACT

To gain a better understanding of disintegration actions, 11 different disintegrants were tested. Model tablets were prepared with various preparation conditions, and their disintegration time and tensile strength were measured. The present study also investigated various physicochemical properties of the model tablets and disintegrant powders, including wetting time, water absorption ratio, particle size, morphological observation, swelling property, and T_2 relaxation time (T_2). The experimental data were thoroughly analyzed using self-organizing map (SOM) clustering. The test disintegrants were classified into four distinct clusters. It is worth noting that superdisintegrants, including croscarmellose sodium (Ac-Di-Sol), sodium starch glycolate (Glycolys), and crospovidone (Kollidone CL-F and Polyplasdon XL-10), were assigned to clusters different from those of normal disintegrants. Furthermore, SOM clustering suggested the latent contributions of factors to the disintegration actions. The disintegrant content had a significant impact on the disintegration actions. Furthermore, the T_2 measurements indicated that the interaction mode of crospovidone with water was different from those of cellulose- and starch-based disintegrants. The evidence obtained is valuable information for the formulation design of tablets.

1. Introduction

To manufacture orally administered compacted tablets, in addition to the active pharmaceutical ingredient (API), a wide variety of excipients is normally incorporated into the tablets [1]. According to the intended main functions, excipients to be incorporated into tablets are subcategorized into different groups. These include disintegrants, fillers, binders, glidants, lubricants, matrix formers, antiadherents, flavoring agents, and colorants [1]. Among these, a disintegrant is the most important excipient for determining the disintegration property of tablets. Tablet disintegration can be understood as the first stage in the bioavailability cascade including drug release and absorption from the gastrointestinal tract.

Excipients that have a hydrophilic but insoluble nature in water or gastrointestinal fluids are considered suitable as disintegrants [2]. Currently, a wide variety of excipients, especially starch- and cellulose-based substances, are used as disintegrants [2,3]. For example, corn starch, partially pregelatinized starch, microcrystalline cellulose, and low-substituted hydroxypropyl cellulose have traditionally been incorporated into tablets as disintegrants. Furthermore, chemical modification of starch, cellulose, and povidone enables us to create excellent disintegrants. In particular, croscarmellose sodium, sodium starch glycolate, and crospovidone are referred to as superdisintegrants because they can achieve excellent disintegration action at much lower concentrations.

To date, various theories have been proposed as the mechanism of disintegration action, including swelling of particles, exothermic wicking reaction, particle deformation recovery, particle repulsion, and heat of interaction [1,2,4,5]. Swelling is commonly accepted as the most important mechanism for tablet disintegration. Swollen disintegrant particles push apart the adjacent components, thereby initiating the breakup of the tablet matrix. Wicking is the ability to draw water into the tablet matrix. It is an essential element for disintegrant activation. Water penetrates the tablet not only through pores, but also along a hydrophilic network by wicking of the incorporated disintegrant particles. It might cause weakening of the tablet structure. It is

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worth noting that these mechanisms are not independent, and each one can influence or be influenced by the other mechanisms. For instance, the wicking can be considered as the pre-request for swelling, deformation recovery, and other proposed disintegration mechanisms [2,5]. Although there are quite a few studies on the mechanisms of disintegrates [2,4,5], they are still complicated, and it therefore remains difficult to fully understand their actions.

Against this background, the present study conducted a comparative study of various disintegrants to gain a better understanding of their disintegration actions. To prepare samples, 11 different test substances were selected from popular disintegrants, and then their model tablets were prepared using different conditions (i.e., change in disintegrant content and compression force in the tabletting process). Afterwards, their properties were measured, and the observed data were thoroughly analyzed using Kohonen's self-organizing map (SOM). Thereby, the disintegrants were ultimately summarized into several clusters to reveal latent relationships between the factors. The present study offers profound insight into disintegration actions of the test disintegrants.

2. Material and methods

2.1. Materials

The disintegrants tested in this study are summarized in Table 1. Low-substituted hydroxypropyl celluloses (L-HPCs) [LH-11 (L11), LH-21 (L21), LH-31 (L31), and NBD-021(NBD)] were purchased from Shin-Etsu Chemical (Tokyo, Japan). Croscarmellose (CMC) [NS-300 (NS)] and croscarmellose calcium (CMC-Ca) [ECG-505 (ECG)] were purchased from Gotoku Chemical (Tokyo, Japan). Croscarmellose sodium (CMC-Na) [Ac-Di-Sol (AC)] was purchased from FMC Health and Nutrition (Philadelphia, PA). Sodium starch glycolate [Glycolys (GLY)] was purchased from Roquette Japan (Tokyo, Japan). Corn starch (CS) was purchased from Nihon Shokuhin Kako (Tokyo, Japan). Crospovidone type A [Kollidon CL-F (KO)] was purchased from BASF Japan (Tokyo, Japan), while crospovidone type B [Polyplasdon XL-10 (PP)] was purchased from ISP Technologies (Ashland, KY). Mannitol (Partec M200) was purchased from Merck Millipore (Billerica, MA). Microcrystalline cellulose (MCC) (Ceolus UF-F711) was purchased from Asahi Kasei Chemicals (Tokyo, Japan). Magnesium stearate (Mg-St) was purchased from Wako Pure Chemical Industries (Osaka, Japan).

2.2. Preparation of model tablets

All ingredients were dried at 75 °C for 24 h and sieved through a 20-mesh screen. The sieved ingredients were accurately weighed and all ingredients except for Mg-St were blended in a polyethylene bag for 1 min. Subsequently, Mg-St was added to the mixture, and then blended together with the mixture in a polyethylene bag for 1 min. The final blend (200 mg) was compressed at 8 or 10 kN into a round tablet, 8 mm in diameter, using a Handtab 100 hydraulic press (Ichihashi-Seiki, Kyoto, Japan). The standard conditions for preparing the model tablets were designed as follows: 5% disintegrant, 85% mannitol (used as filler), 9% MCC (used as binder), and 1% Mg-St (used as a lubricant). Immediately after preparing the tablets, their properties were examined. In addition, some test tablets were stored at 25 °C and 65% relative humidity (RH) for 1 week in a stability chamber (CSH-110; ESPEC, Osaka, Japan), and then changes in their disintegration time (DT) and tensile strength (TS) were evaluated.

Table 1
Disintegrants tested in this study.

Product name	Abbreviation	Common name
Ac-Di-Sol	AC	Croscarmellose sodium (CMC-Na)
Corn starch	CS	Corn starch
ECG-505	ECG	Croscarmellose calcium (CMC-Ca)
Glycolys	GLY	Sodium starch glycolate
Kollidon CL-F	KO	Crospovidone
LH-11	L11	Low-substituted hydroxypropyl celluloses
LH-21	L21	(L-HPC)
LH-31	L31	
NBD-021	NBD	
NS-300	NS	Croscarmellose (CMC)
Polyplasdon XL-10	PP	Crospovidone

2.3. Disintegration time (DT)

The disintegration test was performed according to the JP17 disintegration test for tablets using a disintegration tester (NT-20H; Toyama Sangyo, Osaka, Japan) and water as a solvent at 37 °C. DT was defined as the interval required for a tablet or its particles to disappear completely from the tester net.

2.4. Tensile strength (TS)

The hardness of the tablets was determined using a Tablet Hardness Tester (Portable checker PC-30; Okada Seiko, Tokyo, Japan). TS was calculated as:

$$\mathrm{TS} = \frac{2F}{\pi dt} \tag{1}$$

where F is the maximum diametric crushing force, and d and t are the diameter and thickness of the tablet, respectively.

2.5. Wetting time and water absorption ratio

The wetting time (WT) and water absorption ratio (AR) were measured according to a method described by Bi et al. [6]. A piece of paper towel folded twice was placed in a small culture dish (5.5 cm internal diameter) containing 6 mL of purified water. A model tablet was placed carefully in the center of the dish. The time required for the water to cover the entire surface of the tablet was designated the WT. The AR for the tablets, a variable describing how much water is retained in the tablet when the wetting process is complete, was calculated as follows:

$$AR = \frac{W_a - W_b}{W_b} \times 100 \tag{2}$$

where W_a is the weight after wetting and W_b is the weight before wetting.

2.6. Particle size distribution of disintegrant powders

The mean particle size (d50) of each disintegrant powder was determined from the distribution of the particle sizes using a laser scattering apparatus with dry dispersion unit (Malvern Mastersizer 3000; Malvern Instruments, Worcestershire, UK). The input pressure was below 0.5 bar.

2.7. T_2 relaxation time

A disintegrant powder was dispersed in purified water at 10 mg/mL, and then left for at least 6 h at room temperature to swell the disintegrant particle fully. Immediately after vortexing the sample, the T_2 relaxation time (T_2) of the suspensions was measured by pulse NMR (Acorn area; Xigo Nanotools, Bethlehem, PA) at a ^{1}H frequency of 13 MHz at 29 °C. The pulse sequences used for measurement of ^{1}H T_2s (spin–spin relaxation time) followed the Carr–Purcell–Meiboom–Gill method. The time between each pulse, or τ spacing, was 0.5 ms, averaging 1 scan with the recycle delay was 6–12 s depending on the sample. The measurement of the T_2 was triplicated.

2.8. Swelling property of disintegrant

The same suspensions (40 mL) for use in the T_2 measurement were prepared in glass vessels, and left to stand for a couple of hours at room temperature, resulting in the accumulation of the swollen disintegrant particle in the bottom of vessel. The thickness of the swollen layer was measured, and then the value was employed as the swelling property of the disintegrants.

2.9. Scanning electron microscope observation

The morphology of disintegrant powders was characterized using a scanning electron microscope (SEM) (Hitachi Miniscope TM3000; Hitachi High-Technologies, Tokyo, Japan). The samples were placed on carbon tape without evaporated gold coating.

2.10. SOM clustering

Viscovery SOMine software (version 4.0; Eudaptics Software, Vienna, Austria) was used for SOM clustering. The data for analysis consisted of 33 individual data sets (11 disintegrants, n = 3). Each data set was composed of 13 attributes including DTs and TSs obtained under four different experimental conditions, WT, AR, T_2, swelling, and d50. In order to categorize the data sets into several clusters in terms of their disintegration actions, this study used the DTs as key attributes. They include the DT of standard tablets and % changes in DT as a function of disintegrant contents, compression force, and 1 week of storage. This software enables to prioritize the attributes by controlling the priority index; the index of the key attributes were set at 1, while those of the other attributes were set at 0. The SOM clustering was performed based on the SOM–Ward method. This software offers several clustering techniques including SOM-Ward, Ward, and SOM-Single-Linkage. Of these techniques, SOM-Ward was used for SOM clustering because it is considered to be the most efficient.

3. Results

3.1. Changed behavior of DT and TS with changing factors

The DT and TS of standard tablets are presented in Fig. 1 and shown in supplemental material (see Table s1). Various DT values were observed for the test tablets. AC-, GLY-, and KO-containing tablets disintegrated within a short period; 59.3 ± 4.2 s for AC, 99.7 ± 3.1 s for GLY, and 62.3 ± 0.6 s for KO, respectively. By contrast, the DT of the CS-containing tablet was integral for markedly longer than that of the other tablets, taking over one thousand seconds to disintegrate (1304 ± 174 s). The observed TS values were relatively close, ranging from 2.5 to 3.5 MPa. Crospovidone (KO and PP)-containing tablets possessed relatively low TS: 2.69 ± 0.04 MPa for KO and 2.61 ± 0.07 MPa for PP, respectively.

In addition to the standard tablets, we prepared test tablets with 10% of disintegrant contents or at a compression force of 8 kN. To facilitate comparison of the effects of these formulation factors, the experimental values of DT and TS were expressed as % changes from the standard tablet levels (Fig. 2). As a whole, DT was obviously decreased with increases in the disintegrant content and decreases in the compression force. The effect of the disintegrant content seemed to be higher than that of the compression force, because most samples showed a substantial decrease in DT. Particularly, samples containing CS, NS, and PP reached nearly 20% of the standard tablet levels. The compression force had a great impact on the samples containing CS, L-HPCs (L11, L21, L31, and NBD), and NS; they decreased to less than 50% with decreases in the compression force from 10 kN to 8 kN. In addition, some samples including AC, ECG, and GLY were not affected by changing these factors, which is probably because the DTs of the standard tablets were sufficiently low and did not decrease any further. The effects of the factors on TS appeared to be smaller than those on DT. The TS of the samples containing L11, L21, and GLY was sensitive to changes in compression force; these values decreased to less than 80% of the level found in standard tablets. Furthermore, the sample containing L21 also showed a substantial decrease in TS by changing the content; it reached nearly 60% of the level found in standard tablets.

The present study investigated the changes in DT and TS induced by shelf storage. Before this study began, the moisture absorption behavior accompanying storage was monitored; namely, the samples were stored at 25 °C and 65% RH, and changes in weight were monitored. All tablets reached a full saturation state of moisture absorption within a couple of days, and the weight increase at the end of this experiment amounted to around 1% (supplemental materials, see Fig. s1). Based on this result, a shelf period of 1 week was chosen. Fig. 3 shows % change in tablet properties from the initial level to after 1 week of storage. With regard to DT, a substantial decrease was observed in the samples containing L21, L31, NS, and PP. By contrast, in some samples (GLY and KO-containing tablets), DTs were increased after 1 week of storage, suggesting that the change in behavior of DT accompanied by storage seemed more complicated than that shown in Fig. 2. Chowhen also reported an increase in DT after storage at a RH of 93% [7]. Structural changes of the incorporated disintegrant, such as expansion or contraction, have been mentioned as a possible reason for these findings. The TS of most samples was obviously decreased after 1 week of storage. In particular, a substantial decrease (27.9 ± 1.6%) of the initial level was observed in the sample containing KO.

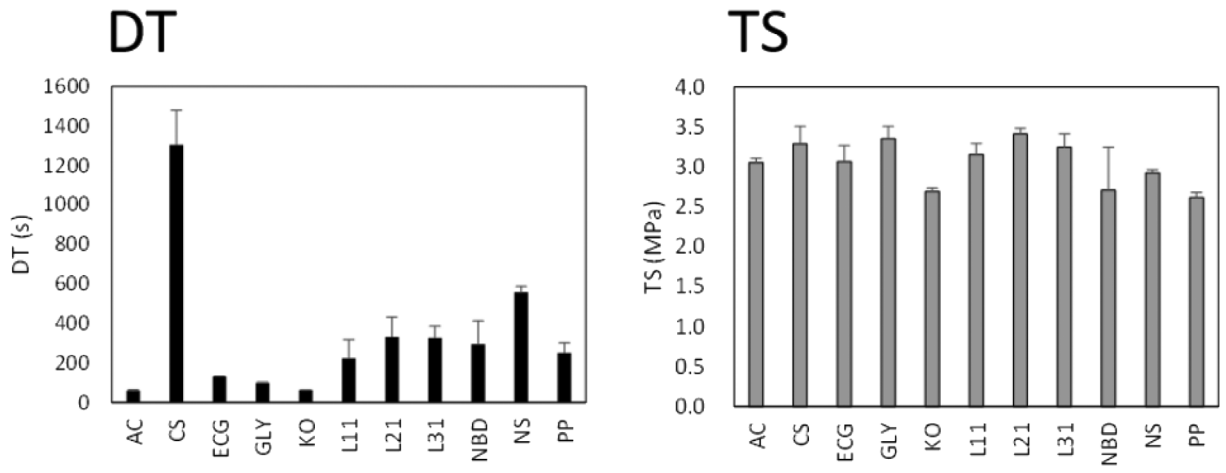

Fig. 1. Disintegration time (DT) and tensile strength (TS) of standard tablets.
The standard test tablets were prepared using the following conditions: 5% disintegrant, 85% Man, 9% MCC, 1% MgSt, 10 kN of compression force (n = 3, mean ± SD).

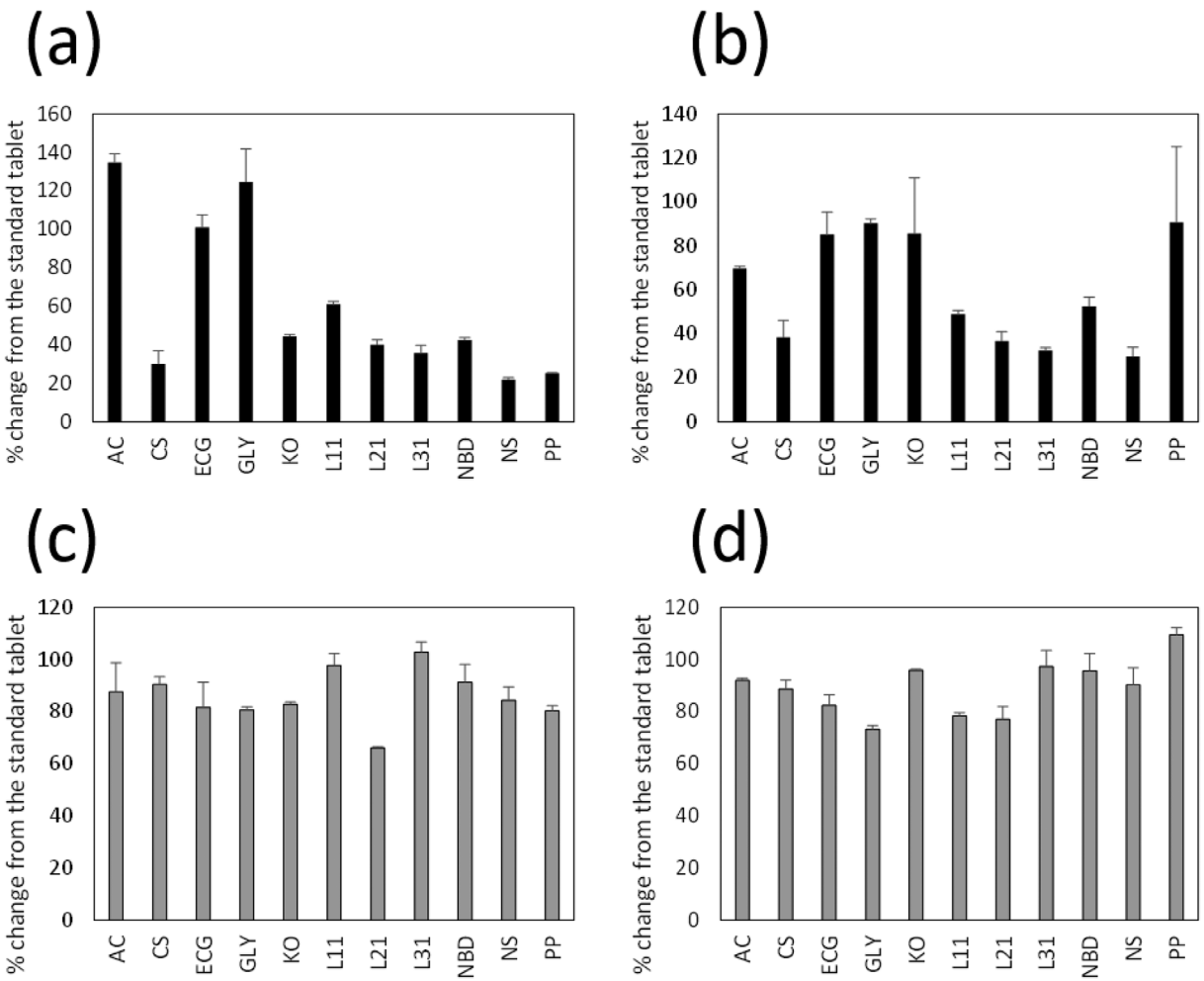

Fig. 2. Changes in disintegration time (a, b) and tensile strength (c, d) caused by changes in formulation factors of the test tablets.
The test tablets of (a) and (c) were different from the standard tablets in terms of disintegrant contents (10%), while those of (b) and (d) were prepared with higher compression force (8 kN). Each value represents the % change from the standard tablets (n = 3, mean ± SD).

3.2. Physicochemical properties of the model tablets and disintegrant powders

In addition to DT and TS, various physicochemical properties were investigated (Fig. 4). The longest WT (606.0 ± 4.4 s) was observed for a CS-containing tablet. By contrast, the wetting of AC- and KO-containing tablets was completed within a short period, up to 300 s. The WTs of tablets containing different L-HPCs (L11, L21, L31, and NBD) were consistent with each other, 352.3 ± 20.8, 355.7 ± 30.4, 399.7 ± 13.7, and 383.0 ± 15.1 s for L11, L21, L31, and NBD, respectively. The largest AR, 1.69 ± 0.15, was observed for a GLY-containing tablet, while the smallest value (0.33 ± 0.02) was for a CS-

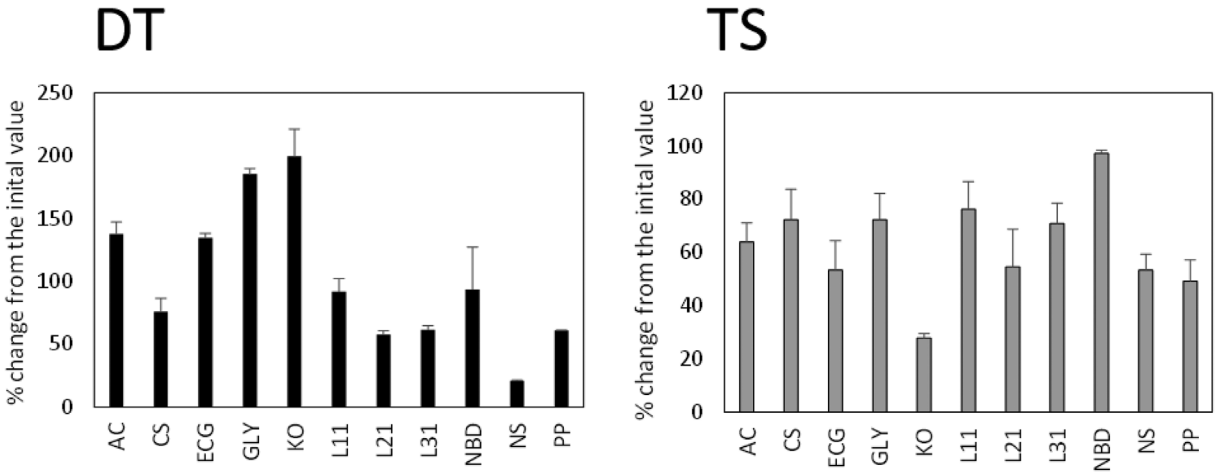

Fig. 3. Changes in disintegration time (DT) and tensile strength (TS) of the standard tablets after 1 week of storage at 25 °C and 65% RH.
Each value represents the % change from the freshly prepared tablets (n = 3, mean ± SD).

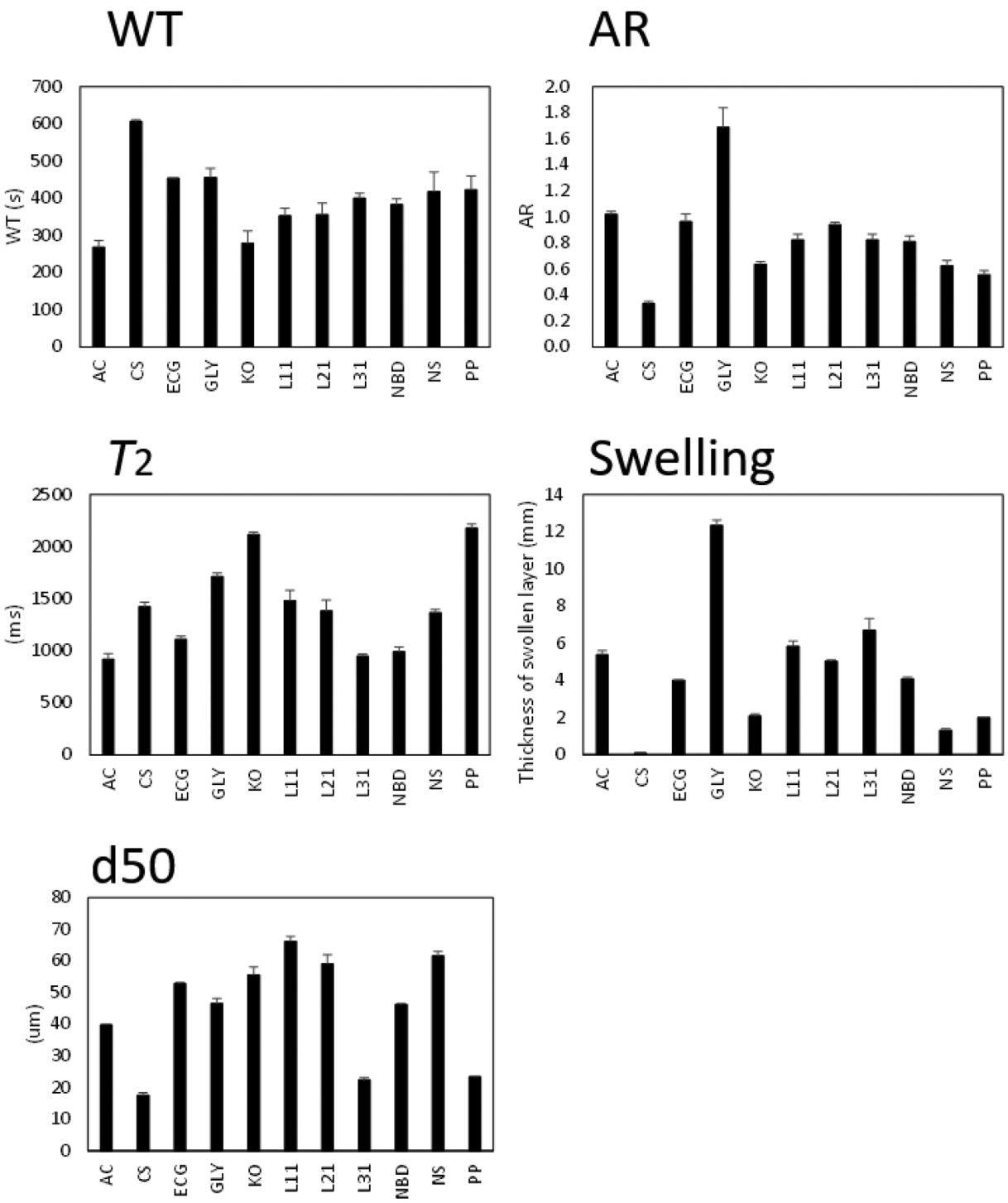

Fig. 4. Physicochemical properties of the standard tablets and disintegrant powders. Wetting time (WT), and water absorption ratio (AR) were tablet properties, while T_2 relaxation time (T_2), swelling, and the mean particle size (d50) were disintegrant powder properties (n = 3, mean ± SD).

containing tablet. The correlation coefficient between WT and AR was not high, –0.1934 (supplemental materials, see Fig. s2), suggesting that these behaviors were independent. Regarding the T_2 of disintegrant aqueous suspensions, the longest values were observed from crospovidone (KO and PP). The differences, 2115 ± 25 and 2176 ± 39 ms for KO and PP, were not significant statistically. By contrast, short values were observed from AC, L31, and NBD; the shortest value (917 ± 54 ms) was observed from AC. The disintegrants have a hydrophilic but insoluble nature in water, so the swollen disintegrant particles can create a swollen layer in the bottom of the vessel. The largest thickness (12.3 ± 0.3 mm) was observed from GLY. By contrast, the CS powder seemed not to be swollen. It is worth noting that a strong association was found between the swelling and AR; the correlation coefficient was extremely high, 0.927 (supplemental materials, see Fig. s2). To understand the morphological properties of disintegrants, SEM images were acquired (Fig. 5). Cellulose-based substances (i.e., AC, ECG, L11, L21, L31, NBD, and NS) appeared to be fibrous by nature. CS starch-based particles were angular, while GLY particles were rounded smoothly. Crospovidones, KO and PP, showed irregular surfaces. The mean particle size distribution, d50, was also

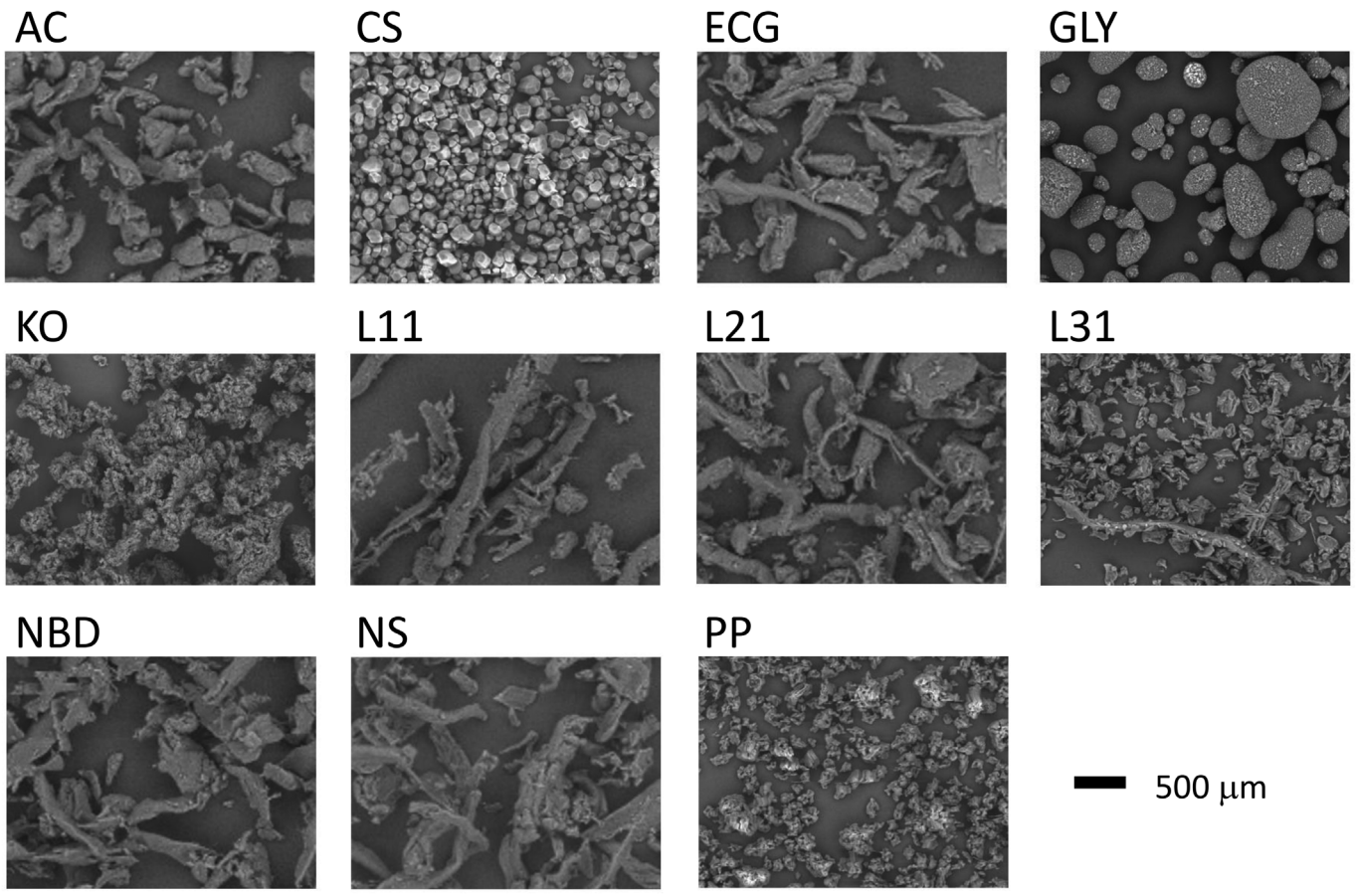

Fig. 5. SEM images of disintegrant powders.

measured. In accordance with SEM observations, CS, L31, and PP powders showed smaller particle sizes, 17.6 ± 0.8 μm for CS, 22.4 ± 0.8 μm for L31, and 23.4 ± 0.1 μm for PP (see Figs. 4 and 5).

3.3. SOM analysis for characterization of the disintegration effects of each disintegrant

The observed data were analyzed using SOM clustering. According to SOM (Fig. 6a), the data sets were classified into four distinct clusters. The individual data sets were directly labeled on the SOM. The disintegrants were assigned to the clusters based on the data distribution on the SOM. The data sets concerning NBD and PP were separately distributed in different clusters. To handle this issue, this study regarded their cluster as being a cluster possessing a larger number of data sets. (e.g., in the case of NBD, 2 in 3 data sets were distributed in cluster 2, while 1 in 3 were distributed in cluster 3; therefore, it was assigned to cluster 2). Consequently, AC, ECG, and GLY were assigned to cluster 1, L-HPCs (L11, L21, L31, and NBD) and NS were assigned to cluster 2, crospovidones (KO and PP) were assigned to cluster 3, and CS was assigned to cluster 4.

Fig. 6b shows SOM feature maps. The lowest DT of the standard tablets was observed from clusters 1 and 3. The DT of cluster 4 was markedly higher than that of the other clusters. The disintegrant content seemed to have a great impact on the DT of clusters 2, 3, and 4, because a substantial decrease in the % change was found from the feature maps. The DTs of clusters 2 and 4 were also decreased by the lower compression force and 1 week of storage. The feature maps of the other physicochemical properties are shown in Fig. 6b. The map patterns concerning TS seemed completely different from those of DT; thus, no latent relationship was observed. In addition, the AR patterns and swelling properties were entirely consistent; this result fully reflected the high correlation coefficient. Furthermore, T_2 values of cluster 3 were obviously longer compared to the other clusters.

4. Discussion

The present study sought to gain a better understanding of the disintegration actions of various disintegrants. The test substances were selected from disintegrants popularly used for commercial products. GLY (sodium starch glycolate), KO and PP (crospovidones), and AC (CMC-Na) are referred as “superdisintegrants” [3,8].

To characterize their disintegration actions, the present study made use of SOM analysis. SOM is a feedforward-type neural network model regarded as a powerful tool for data mining. It enables analysis of multidimensional data by expressing them as a two-dimensional map [9]. Applications of the SOM have been reported across a range of pharmaceutical and medical fields [10–12]. We also have been applying this promising technique for the formulation design of pharmaceuticals [13–15]. The SOM consists of an array of nodes, and each node possesses the same number of parametric reference vectors as the tutorial data set [9]. In SOM, the adjacent nodes are associated with each other; thus, the distance between the nodes expresses the degree of similarity between them, and neighboring nodes have similar properties. SOM analysis provides us with sensible distinct clusters by taking account of the changed behavior of input vectors. Furthermore, we can perceive the latent relationships among factors by comparing the patterns of the maps and the spatial position of each node.

The present study performed SOM clustering using the parameters of the disintegration actions as key attributes, and then classified the test disintegrants into four distinct clusters. The distinct disintegration actions of each cluster were well characterized. Cluster 1 had short DTs that were relatively stable in disintegrant content, compression force,

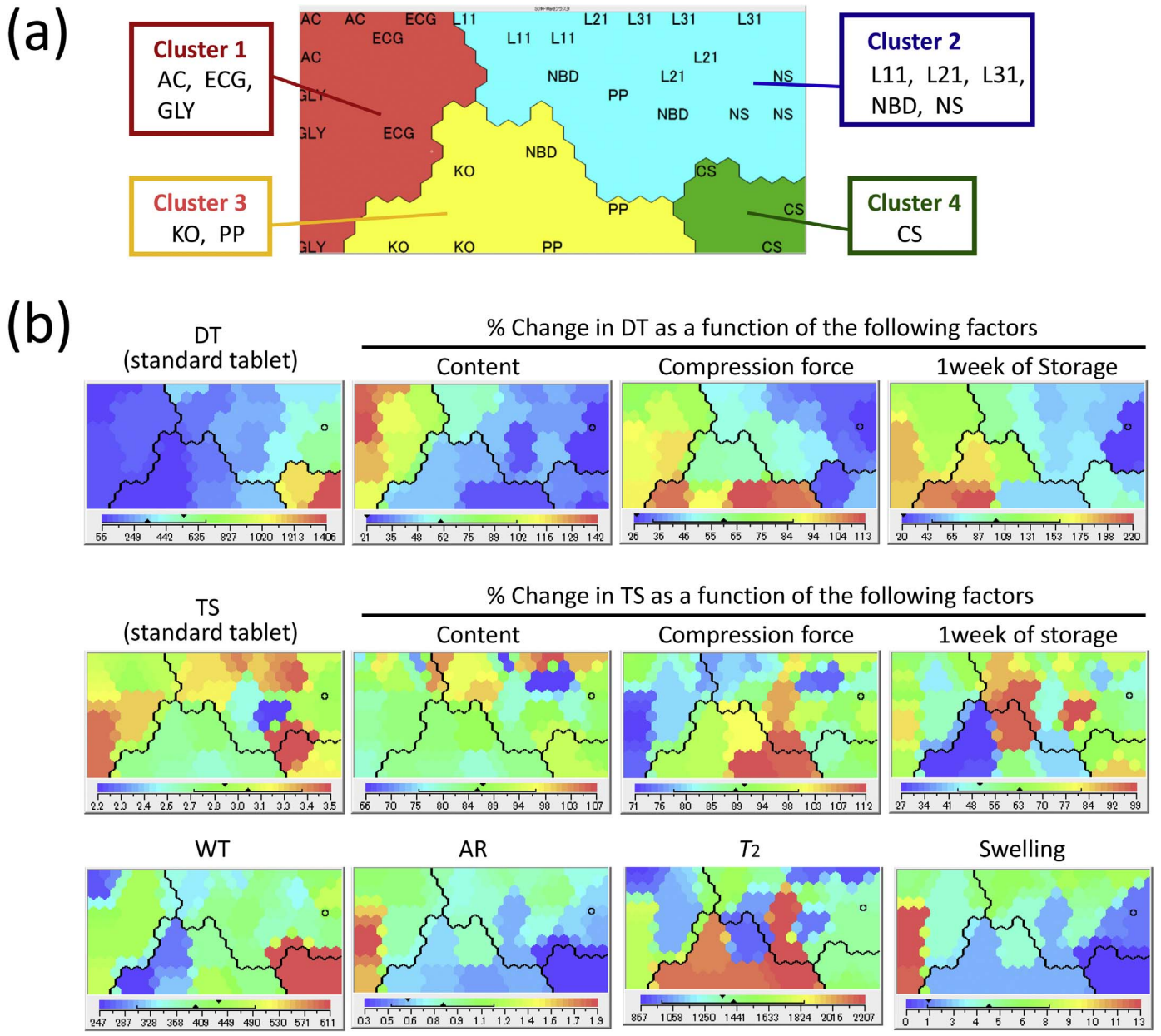

Fig. 6. (a) SOM and (b) SOM feature maps concerning the disintegration actions of different disintegrants. The SOM clustering was performed using the DT of the standard tablets and % change in DT as a function of disintegrant content, compression force, and 1 week of storage (n = 3) as tutorial data sets. Each tutorial data set was labeled on the nodes of the SOM (a) to express the data distribution. SOM feature maps (b) show each variable in color: red regions represent higher and blue regions lower values. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and storage for 1 week. Compared with cluster 1, cluster 2 had slightly longer DTs and was substantially affected by the changes in all factors tested. Cluster 3 DTs showed the lowest level by at least as much of that of cluster 1, and they were sensitive to the disintegrant content. Cluster 4 was formed by the CS data sets having extremely long DT. In recent years, orally disintegrating tablets (ODTs) have attracted considerable attention because they are patient friendly dosage forms. ODTs are easy to swallow and can be taken orally with or without water [16,17]. Considering that ODTs are generally designed to disintegrate in the mouth without water in 180 s or less [18], clusters 1 and 3 seemed to have sufficient disintegration actions. It is worth noting that the superdisintegrants tested were sharply distinguished from the normal disintegrants; AC and GLY were assigned to cluster 1, while crospovidones (KO and PP) formed cluster 3. It is widely accepted that AC and GLY have excellent disintegration properties by different mechanisms [19]. The disintegration action of GLY is mostly caused by its outstanding swelling property. By contrast, AC acts mainly by its rapid wicking capability; according to its fibrous structure, and draws water swiftly into the tablet matrix with resulting excellent disintegration action. Since the key attributes for the present SOM clustering did not contain any information about the disintegration mechanisms, the above difference is not attributed to the resultant clusters. Despite the different mechanisms, AC and GLY showed the relatively close disintegration actions.

SOM clustering also suggested the factors affecting DT by comparing the patterns of their feature maps. WT and AR are usually compared with the disintegration actions in the relative studies, because they are thought to associate with DT. For example, Hooper et al. conducted a comparative study on commercial tablets, and close correlation between WT and DT were shown from the most tablets tested [20]. In the present study, although the patterns of the feature maps were not so similar, the correlation coefficient of the tutorial data was

relatively high, 0.7230 (supplemental materials, see Fig. s2), suggesting a potential relationship between WT and DT. From the changed behavior of WT and AR, differences in the mode of action of the superdisintegrants were fully characterized. For instance, the shortest WT was observed from an AC-containing tablet. It represents the rapid water wicking capability as mentioned above [19]. Furthermore, a model tablet containing GLY showed the highest AR. That is because GLY is a swelling type disintegrant that enables greater water retention. Iwao et al. monitored time-dependent changes in AR of model tablets, and reported that GLY-containing tablets showed a much higher AR than the others [21]. From other relative articles, sodium starch glycolate (e.g., GLY) has always shown a much higher swelling capacity [8,22]. We note that an extremely high correlation was observed between AR and the swelling of the disintegrant powder (correlation coefficient = 0.927). AR is considered to be closely related to the inner structure of the tablet and the chemical properties of excipients such as hydrophilicity [6]. We consider that the swelling property of the disintegrant powder was the predominant factor of AR in the present study. In addition to the actions of superdisintegrants, SOM clustering clearly visualized the low hydrophilicity of CS (cluster 4). It showed the lowest AR and the longest WT, indicating that it took a longer time to absorb water. The longest DT of CS-containing tablets was mostly because of its low hydrophilicity.

We also note that this study investigated the interaction of disintegrant particles with water by measuring the T_2 of disintegrant suspensions. NMR is one of the most powerful techniques for determining molecular mobility and dynamic molecular interactions [23,24]. In the present study, we regarded the T_2 as an index to estimate the interaction between disintegrant and water; shorter T_2 indicated that the water molecular mobility was restricted more tightly by the interaction with the disintegrant particles. As a result of the comparative experiments, the longest T_2 values were observed for crospovidones. This study confirmed that the interaction of crospovidone with water is distinct from that of cellulose- or starch-based substances; they had a weaker interaction with water molecules. Although further investigation is required, there is a possibility that the weak interaction plays an important role in the excellent disintegration actions of crospovidone. As a possible contribution, the weak interaction helps to draw a larger amount of water into the deeper part of tablet matrix, resulting in enhanced disintegration.

5. Conclusions

The present study provides enhanced technical knowledge concerning the disintegration actions of different disintegrants. Using SOM clustering, we could classify the disintegration actions of test disintegrants into four distinct clusters. The actions of the superdisintegrants were sharply distinguished from those of standard disintegrants. Furthermore, the latent relationships between the disintegration actions and physicochemical properties were suggested from the SOM feature maps. This study will provide valuable information for the formulation design of tablets.

Conflict of interest

The authors declare that they have no financial or noncompeting interests concerning this manuscript. The Department of Pharmaceutical Technology, University of Toyama, is an endowed department, supported by an unrestricted grant from Nichi-Iko Pharmaceutical Co (Toyama, Japan).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jddst.2017.10.002.

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