# A Novel Method for Predicting Disintegration Time in the Mouth of Rapidly Disintegrating Tablet by Compaction Analysis Using TabAll

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**A tableting process analyzer (TabAll) was used to predict disintegration time in the mouth of rapidly disintegrating tablet. Analyzer profiles recorded upper punch displacement and die wall force encountered during tablet processing. Changes in the mixing ratio of spherical sugar granules and microcrystalline cellulose or lactose affected upper punch displacement and die wall force profiles. Analysis of the compaction process revealed a strong association between disintegration time in the mouth and stationary time, relaxation time of upper punch displacement, and relaxation time of die wall force; disintegration time in the mouth decreased as the three parameters increased. Thus, analysis of the compaction process is useful for predicting disintegration time in the mouth of rapidly disintegrating tablet, which can assist the formulation of new rapidly disintegrating tablets.**

**Key words** compaction analysis; rapidly disintegrating tablet; disintegration time; tableting process analyzer

Reports indicate that elderly patients often experience difficulty taking some medications formulated as powders, tablets, or capsules due to a decline in swallowing ability.[1,2] Rapidly disintegrating tablets are a convenient oral dosage form for patients who have difficulty swallowing conventional tablets or capsules, because the tablet can be swallowed with a small amount of water or saliva. However, rapidly disintegrating tablets are formulated empirically, making it difficult to optimize tablet formation because few studies have focused on the disintegration mechanism and formulation design. Previously, we reported that rapidly disintegrating tablets can be prepared by direct compression method using microcrystalline cellulose (MCC) in combination with low-substituted hydroxypropylcellulose or spherical sugar granules.[3,4] Disintegration time is particularly important for rapidly disintegrating tablets. Measurement of *in vitro* disintegration time typically involves the JP XIV disintegration test apparatus. However, this method is not suitable for rapidly disintegrating tablets, because the disintegration involves only a small amount of water or saliva. Furthermore, the *in vivo* disintegration test cannot ethically be used when formulating potent drugs to maintain the safety of the volunteers. Predicting disintegration time in the mouth is needed when formulating new rapidly disintegrating tablets. Therefore, we evaluated factors related to disintegration time in the mouth. Crushing tolerance and porosity have been reported to be linked to tablet disintegration,[5,6] however these parameters are not closely correlated with disintegration time in the mouth. We focused on an analysis of the compaction process using a single punch machine equipped with several force analysis elements, and found a novel factor that predicted *in vivo* disintegration time of rapidly disintegrating tablets.

## Experimental

**Materials** MCC (Avicel® PH101, PH102, PH-M-25, and Ceolus® KG802, Asahi Kasei Chemicals Co., Ltd., Tokyo), crospovidone (NF grade, Polyplasdone XL®, ISP Japan Co., Ltd., Tokyo), purified D-mannitol spheres (NP108, Nonpareil-108®, Freund Industry Co., Ltd., Tokyo) and lactose for direct compression (DR, Dilactose®R, Freund Industry Co., Ltd., Tokyo) were kindly donated. Magnesium stearate (Mg-St) was purchased from Wako Pure Chemical Industries, Osaka. All reagents were of analytical grade.

**Tablet Preparation** NP108 and MCC or DR were mixed at various weight ratios (5 : 5 to 1 : 9) and then Mg-St (1%) was added. As a disintegrant, 10% crospovidone was added to the mixture of NP108 and DR. A tableting process analyzer (Model N-30EX, TabAll, Okada Seiko Co., Ltd., Tokyo) equipped with flat-faced punches 8 mm in diameter was employed (press speed, 10 tablets/min). The mixture was compressed at 5 kN. The compaction of the material was evaluated by TabAll, which can measure seven profiles during the compaction process: upper and under punch displacement, upper and under punch forces, die wall force, ejection force, and scraper pressure. Data were recorded using the software (DAATSU II, Okada Seiko Co., Tokyo).

**Measurement of Disintegration Time in the Mouth** Disintegration time in the mouth was determined according to the method of Ishikawa *et al.*[4] Briefly, three healthy volunteers, who supplied informed consent, were randomly assigned a prepared tablet and the time required for disintegration of the tablet in the mouth, without chewing and without drinking water, was recorded. If the tablet did not disintegrated within 120 s, the disintegration time was defined as greater than 120 s. Three measurements were averaged to obtain an individual oral disintegration time.

## Results and Discussion

Crushing tolerance and porosity have been reported to be linked to the disintegration of tablets,[5,6] although they do not strongly correlate with disintegration time in the mouth of rapidly disintegrating tablet. Disintegration time in the mouth is influenced by powder compactibility. Therefore, it is important to investigate the parameters of the compaction process that affect disintegration time in the mouth. The upper punch displacement and die wall force profiles from rapidly disintegrating tablets and conventional tablets were extremely different. Profile differences also were observed

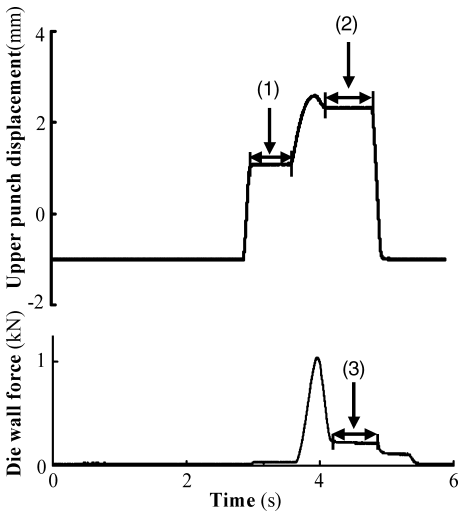


Fig. 1. Change in Upper Punch Displacement and Die Wall Force during Compaction

(1) Stationary time of upper punch displacement (STP). (2) Relaxation time of upper punch displacement (RTP). (3) Relaxation time of die wall force (RTD).

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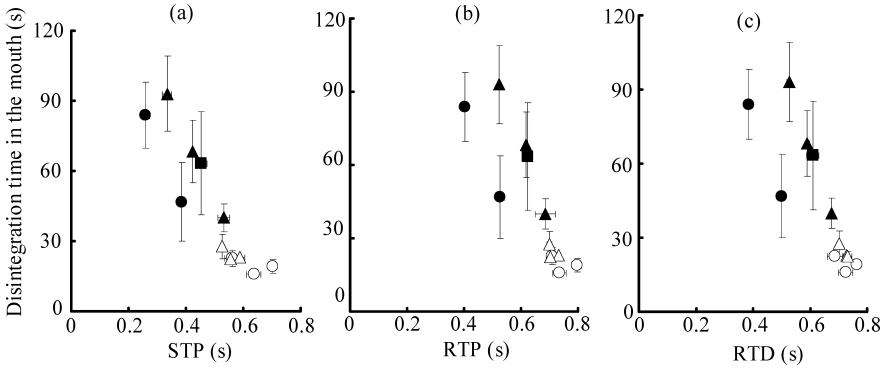


Fig. 2. Relation between STP (a), RTP (b), and RTD (c) and Disintegration Time in the Mouth

Correlation coefficient ($r$): (a), $r=-0.907$; (b), $r=-0.862$; (c), $r=-0.859$. Each point represents the mean±S.D. of three experiments. Symbols: ●, PH101; ▲, PH102; ■, KG802; ○, PH-M-25; △, DR.

for different formulations of rapidly disintegrating tablets. Examples of the profiles for upper punch displacement and die wall force are shown in Fig. 1. Three parameters were defined: (1) stationary time of upper punch displacement (STP), (2) relaxation time of upper punch displacement (RTP), and (3) relaxation time of die wall force (RTD). STP, RTP, and RTD varied among the formulations, leading to an investigation of the relations between the three parameters and disintegration time in the mouth. Figure 2 shows the relations between disintegration time in the mouth and (a) STP, (b) RTP, and (c) RTD. In all formulations, the value of the three parameters increased with an increase mixing ratio of NP108, while disintegration time in the mouth decreased with an increase in the three parameters (correlation coefficient ($r$) values : $-0.907$, $-0.862$ and $-0.859$ for (a), (b) and (c), respectively). From these results, it is presumed that (a) is the best parameter to predict disintegration time in the mouth for rapidly disintegrating tablets. The negative correlation between disintegration time in the mouth and the three parameters indicate that a common factor influences the three parameters and disintegration time in the mouth. Crushing tolerance and porosity of tablets are influenced by the compaction properties (elastic, plastic deformation, and fragmentation) of pharmaceutical materials.[7] Values of STP, RTP, and RTD were different for potassium chloride (plastic deformation) and crospovidone (elastic deformation), indicating these factors are influenced by compaction properties. Thus, disintegration time in the mouth is closely related to the compactibility of powders.

We conclude that an analysis of compaction using TabAll is useful for predicting disintegration time in the mouth for rapidly disintegrating tablets during formulation. Additional analyses of the compaction process using various excipients and drugs are being conducted to obtain more information about its relation to STP, RTP, and RTD.

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