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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.