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An easy-to-use approach for determining the disintegration ability of disintegrants by analysis of available surface area

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ABSTRACT

With the aim of directly predicting the functionality and mechanism of disintegrants during the disintegration and dissolution of tablets, we investigated an analysis method based on available surface area, which is the surface area of a drug in a formulation in direct contact with the external solvent during dissolution. We evaluated the following disintegrants in this study: sodium starch glycolate (Glycolys), crospovidone (Kollidon CL), carboxymethylcellulose calcium (CMC-Ca), low-substituted hydroxypropylcellulose (L-HPC), and croscarmellose sodium (Ac-Di-Sol). When disintegrant was added to a 50% ethenzamide tablet formulation, an increase in the dissolution rate dependent on disintegrant concentration was observed, according to the type of disintegrant. In addition, the available surface area also differed between disintegrants. For Glycolys, CMC-Ca, and Ac-Di-Sol, a rapid increase in available surface area and a large increase in maximum available surface area (S_{max}) were observed due to high swellability and wicking, even when the disintegrant concentration was only 1.0%. In contrast, for Kollidon CL and LH-21, a gradual increase in available surface area was observed, depending on the disintegrant concentration. To evaluate the disintegrant ability, Δt_{max} and ΔS_{max} were calculated by subtracting peak time (t_{max}) at 5.0% from that at 1.0% and subtracting S_{max} at 1.0% from that at 5.0%, respectively, and it was found that the water absorption ratio had strong negative correlations with Δt_{max} and ΔS_{max}. Therefore, this study demonstrates that analysis of only available surface area and parameters thereby obtained can directly provide useful information, especially about the disintegration ability of disintegrants.

1. Introduction

The disintegration of a tablet can be regarded as the first step toward the bioavailability and pharmaceutical action of an active ingredient. To achieve sufficient disintegration, a disintegrant must normally be added to the tablet formulation. Traditional tablet disintegrants can be classified as starches (e.g., corn, wheat, potato, rice, and pregelatinized starches), macromolecules (e.g., alginic acid, sodium alginate, polacrilin potassium, and guar gum), finely divided solids (e.g., colloidal silicon dioxide and magnesium aluminum silicate), and celluloses (e.g., powdered cellulose, microcrystalline cellulose, carboxymethylcellulose, cross-linked sodium carboxymethylcellulose, methylcellulose, and low-substituted hydroxypropylcellulose). Swelling and wicking are the primary mechanisms of action for tablet disintegrants, but other mechanisms such as deformation recovery, particle repulsion, heat of wetting, and gas evolution, may play a role in the disintegration of particular tablet formulations (Kanig and Rudnic, 1984). Another possibility is that several of these mechanisms act simultaneously.

Respective of the mechanism of action, water uptake has been identified as the necessary first step in any disintegration process (Van Kamp et al., 1986; Caramella et al., 1986). In addition, Colombo et al. (1981, 1988) and Caramella et al. (1986, 1988) have related the disintegration process to the development of a disintegrating force inside the tablet. They concluded that water penetration into an insoluble tablet is accompanied by the development of a proportional force, indicating the relevance of disintegration mechanisms that are capable of force development (Caramella et al., 1986).

At present, a disintegration test is the standard method for evaluating disintegrant functionality. However, this method provides only limited information about disintegration behavior, but no information about drug dissolution from a tablet. Although water uptake into disintegrants is also measured in combination with the disintegration test, the disintegration mechanism cannot be ascertained with certainty from the results. Therefore, to accurately evaluate the functionality and mechanism of disintegrants in the disintegration of tablets, as well as the dissolution behavior of drugs, an alternative method to reflect both in vitro disintegration and dissolution is needed.

Abbreviations: ETZ, Ethenzamide; Glycolys, Sodium starch glycolate; K-CL, Kollidon CL; CMC-Ca, carboxymethylcellulose calcium; L-HPC, low-substituted hydroxypropylcellulose; Ac-Di-Sol, croscarmellose sodium; Mg-St, magnesium stearate.

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Against this background, available surface area ($S(t)$), which is a physicochemical property that a drug in a formulation directly contacts with the external solvent, has attracted attention and can be estimated by using dissolution test results only, as we have reported previously (Kouchiwa et al., 1985). In general, dissolution of solid dosage forms includes disintegration and deaggregation process. Although these processes are further complicated, the use of $S(t)$ can directly represent the drug dissolution from the tablets including the disintegration process. Using the time course of $S(t)$, we elucidated the effect of differences in pharmaceutical processing, such as compression force and formulation, on the dissolution of flufenamic acid (Itai et al., 1986). We also reported that when determining whether a lubricant retards the dissolution of a drug, analysis of $S(t)$ enabled prediction of the dissolution and disintegration behavior of acetaminophen tablets formulated using various lubricants (Uchimoto et al., 2011), suggesting that this analysis can allow precise prediction of the disintegration, dispersion and dissolution of the tablet. Therefore, this analysis is also considered to have a potential to evaluate the disintegration ability of disintegrants.

In the present study, we used five commercially available disintegrants to evaluate a method for analyzing disintegrant behavior on the basis of available surface area, as an alternative to traditional disintegration tests and water uptake measurements.

2. Materials and methods

2.1. Materials

Ethenzamide (ETZ; listed in the Japanese Pharmacopeia 16th Edition (JP16), which was used as the active pharmaceutical ingredient), was kindly provided by Iwaki Pharmaceutical Co., Ltd. (Shizuoka, Japan). Lactose monohydrate (Pharmatose 200M, listed in JP16, used as filler) and microcrystalline cellulose (Avicel PH-102, listed in JP16, used as filler) were kindly provided by DFE Pharmaceutical Co., Ltd. (Tokyo, Japan) and Asahi Kasei Co., Ltd. (Tokyo, Japan), respectively. Hydroxypropylcellulose (HPC-L, listed in JP16, used as binder) was kindly provided by Nippon Soda Co., Ltd. (Tokyo, Japan). Sodium starch glycolate (Glycolys, listed in JP16, Roquette Japan K. K. (Tokyo, Japan)), crospovidone (Kollidon CL (K-CL), listed in JP16, BASF Japan Co., Ltd. (Tokyo, Japan)), carboxymethylcellulose calcium (E.C.G-505 (CMC-Ca), listed in JP16, Gotoku Chemical Co., Ltd. (Tokyo, Japan)), low-substituted hydroxypropylcellulose (LH-21 (L-HPC), listed in JP16, Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan)), and croscarmellose sodium (Ac-Di-Sol, listed in JP16, Dainippon Sumitomo Pharma, Co., Ltd. (Osaka, Japan)) were used as disintegrants. All other reagents used were of the highest grade available from commercial sources, and all solutions were prepared with deionized water.

2.2. Granulation

Lactose monohydrate (140 g) and microcrystalline cellulose (60 g) were mixed for 15 min in a mixer (Fuji Medical Equipment Co., Ltd.). ETZ (200 g) was added to this powder and mixed for an additional 15 min. A total of 150 g of 5.0% (w/v) aqueous solution of HPC-L was then added via a syringe (ss-10sz, Terumo Corporation, Tokyo, Japan), and the mixture was subsequently kneaded for 15 min. Granulation was performed in a rotating squeeze-type granulator with a sieve size of 0.8 mm (Hata Iron Work Co., Ltd. Kyoto, Japan). The granules were dried in an oven at 50 °C for 12–16 h. After drying, the granules were sieved through a 1680 μm sieve, and the granules that did not pass through a 350 μm sieve were collected. This process was repeated several times, and the resultant granules were then mixed uniformly and subjected to experimental analysis.

2.3. Tablet preparation

A total of 8 g of mixture composed of granules, magnesium stearate (Mg-St; specified as a lubricant, listed in JP16), and each disintegrant was manually mixed in a polyethylene bag at a rate of 120 times/min for 2 min. The disintegrant concentrations were 1.0%, 3.0% and 5.0%, and the Mg–St concentration was 0.5%. Tablets were prepared with an oil press (JASCO Co., Tokyo, Japan) using a flat-faced punch of 13 mm in diameter. The tableting force was 10 kN, which was applied for 30 s.

2.4. Determination of apparent solubility

ETZ (1 g) was added to pH 6.8 phosphate buffer (200 mL) at 37 °C, and the mixture was agitated for 10 h. A 2 mL aliquot of this mixture was withdrawn and filtered through a membrane filter (0.45 μm) immediately. The filtered solution was volumetrically diluted, the absorbance at 290 nm was measured on a spectrophotometer (UV-mini, Shimadzu Corporation, Kyoto, Japan), and the concentration of dissolved ETZ was calculated from a calibration curve prepared from standard solutions.

2.5. Determination of the dissolution rate constant per unit area

To determine the dissolution rate constant k, the stationary disk method was used (Agata et al., 2010). An ETZ disk with a diameter of 1.3 cm (surface area: 1.33 cm^2) was prepared by compressing 400 mg of the drug powder at 10 kN. The disk was placed in a JP16 dissolution test apparatus and rotated at 50 rpm in phosphate buffer at pH 6.8 and 37 ± 0.5 °C. Solution (5 mL) was withdrawn at appropriate intervals, and after adequate dilution, the ETZ concentration was determined in the same manner as described in Section 2.4. When the ETZ concentration (C) (mg/L) was plotted versus time (t) (min) and fitted to the experimental data by the least-squares method, the following equation was obtained:

$$C = 0.246t + 1.440 (R^2 = 0.9961). \quad (1)$$

From the Noyes–Whitney equation, the following equation was derived when the surface area was fixed under sink conditions:

$$C = \frac{k \cdot S \cdot Cs}{V} \cdot t, \quad (2)$$

where k is the dissolution rate constant per unit area, S *is* surface area, V is the medium volume, and Cs is the apparent solubility. By comparing the slope between Eqs. (1) and (2), k was then estimated.

2.6. Dissolution test

The dissolution of ETZ from tablets was measured by the paddle method listed in JP16. The test medium was 900 mL phosphate buffer (pH 6.8) at 37.0 ± 0.5 °C, and the paddle rotation speed was 50 rpm. At 1.0, 2.5, 5.0, 7.5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 240, 280, 320 and 400 min, samples (3 mL) were withdrawn, and 3 mL of fresh medium was added after collecting each sample. The solution was then filtered through a membrane filter (0.45 μm). The ETZ concentration was determined in the same manner as described in Section 2.4.

2.7. Determination of time course of the available surface area during dissolution

To determine the time course of the available surface area $S(t)$ as well as the corresponding dissolution rate (C), the following