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Prediction of coning phenomena for irregular particles in paddle dissolution test

Mizuki Higuchi, Shunki Nishida, Yasuo Yoshihashi, Katsuhide Tarada, Kiyohiko Sugano *

Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Toho University, 2-2-1, Miyama, Funabashi, Chiba 274-8510, Japan

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ABSTRACT

The purpose of the present study was to investigate the applicability of the Zwietering equation to predict the occurrence of coning phenomena for non-spherical, porous, and swell-able particles in the paddle dissolution test. For non-spherical particles, the minimum rotation speed at which the coning phenomena disappear (no coning rpm, NC_{rpm}) was appropriately predicted by using the Stokes diameter or the short side length of the particles. For porous and swell-able particles, NC_{rpm} was appropriately predicted by using the Stokes density of the particles. The accuracy of the Zwietering equation was sufficient to be used for development of a dissolution test method.

1. Introduction

The pharmacopeia dissolution tests, such as USP apparatus 2 (the paddle method), are widely used in the pharmaceutical industry (Azarmi et al., 2007; Gray et al., 2009). The configuration of the paddle method often causes the coning phenomena due to insufficient agitation underneath the paddle (Bai and Armenante, 2008; Bai et al., 2007). Therefore, it is important to understand and control the coning phenomena for the Quality-by-Design approach (Lionberger et al., 2008; Yu, 2008; Zhang et al., 2011). The occurrence of coning phenomena depends on the particle size, the particle shape, the effective particle density, the fluid viscosity, the fluid density, the apparatus configurations and the agitation strength.

Previously, we reported that the Zwietering equation (Eq. (1)) can be used to predict the minimum rotation speed at which the coning phenomena disappear (NC_{rpm}: no coning rpm) in the compendium paddle method (Higuchi et al., 2014; Zwietering, 1958).

$$NC_{rpm} = 57 d_p^{0.22} \left(\frac{\rho_p - \rho_f}{\rho_f}\right)^{0.52} \left(\frac{\mu_f}{\rho_f}\right)^{-0.23} \quad (1)$$

where μ_f is the fluid viscosity, ρ_f is the fluid density, ρ_p is the particle density, and d_p is the diameter of particles. In our previous study, this equation was validated for spherical non-porous non-swelling particles. However, the shape of drug particles is usually non-spherical. In addition, some excipients such as disintegrants and porous adsorbents change their effective density when immersed in water (Ingram and Lowenthal, 1966; Kang et al., 2011). The applicability of the Zwietering equation for these kinds of particles has not yet been investigated. The purpose of the present study was to investigate the applicability of the Zwietering equation to predict the occurrence of coning phenomena for non-spherical, porous, and swell-able particles in the paddle dissolution test.

2. Materials and methods

2.1. Materials

Alacepril and tolbutamide were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Ibuprofen was purchased from Hamari Chemicals, Ltd. (Yamagata, Japan). Phenacetin was purchased from YAMAMOTO CHEMICAL IND. CO., Ltd. (Wakayama, Japan). Neusilin® (porous magnesium aluminometasilicate) and Fujicalin® (porous dibasic calcium phosphate anhydrous) were provided by Fuji Chemical Industries Co., Ltd. (Toyama, Japan). PCS® (Pregelatinized starch) was provided by AsahiKASEI chemicals Co., Ltd. (Tokyo, Japan). Primellose® (Croscarmellose sodium) was provided by DFE pharma (Tokyo, Japan). Hydroxypropylmethylcellulose (HPMC SM-4) was provided by Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). Wet sieving was used to control the particle size distribution within a small particle size range. Alacepril, phenacetin, tolbutamide, and ibuprofen were sieved between 90 μm and 100 μm. The particle size ranges of Neusilin®, Fujicalin®, PCS® and Primellose® are shown in Table 4.

* Corresponding author.
E-mail address: kiyohiko.sugano@phar.toho-u.ac.jp (K. Sugano).

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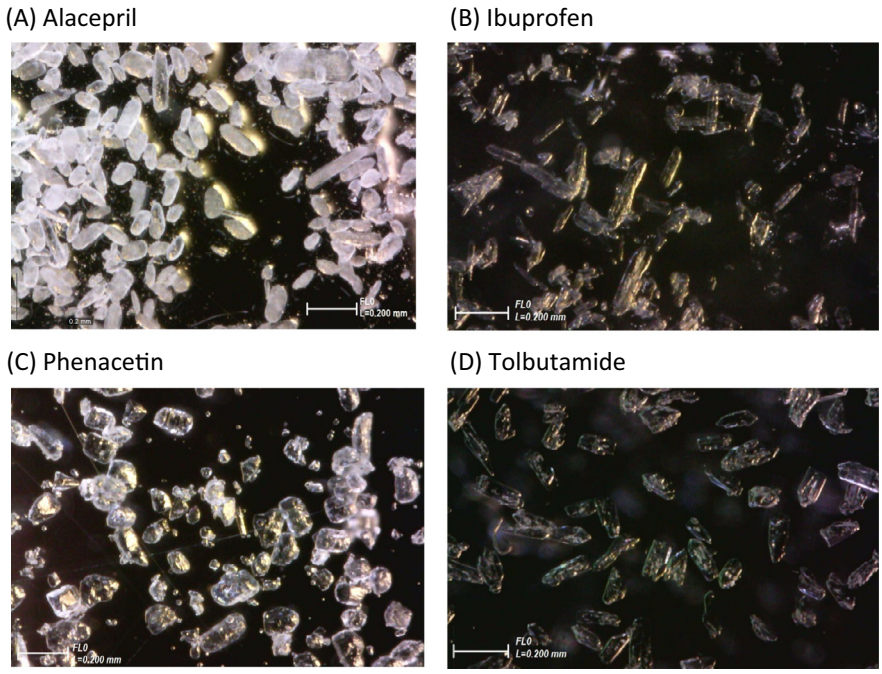

Fig. 1. Photo images of non-spherical particles. (A) Alacepril, (B) ibuprofen, (C) phenacetin, and (D) tolbutamide.

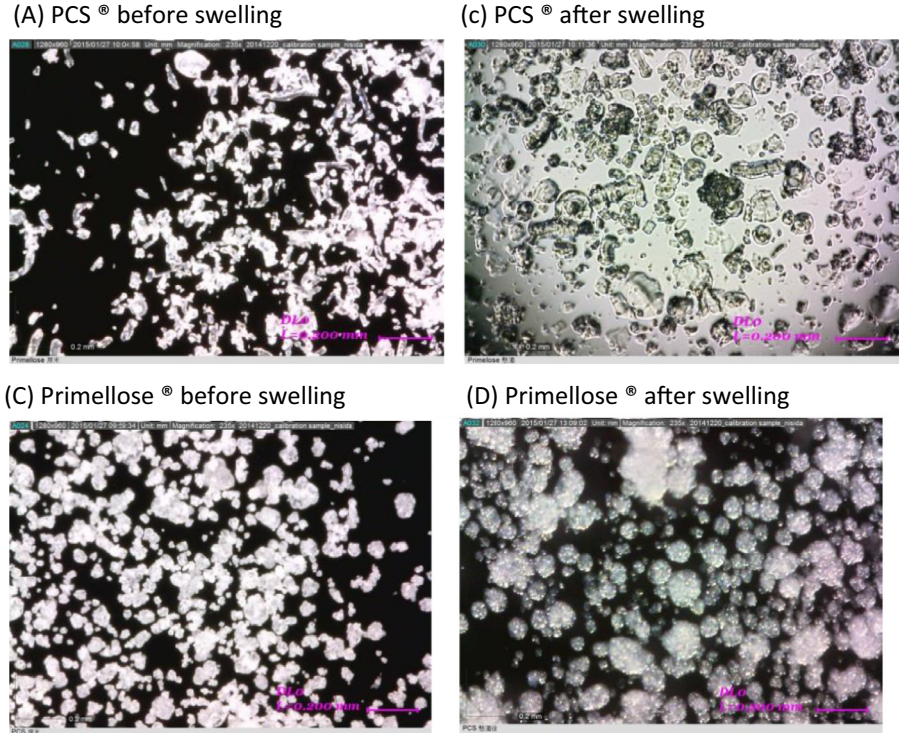

Fig. 2. Photo images of swell-able particles before and after swelling. (A) PCS®, and (B) Primellose®.

2.2. Methods

2.2.1. Optical particle size and shape analysis

The size and shape of non-spherical particles was analyzed by optical microscopy (Dinolite, THANKO) (Figs. 1 and 2). Twenty particles were randomly selected and the short and long side length were measured using graphical analysis software (Dinolite, THANKO).

2.2.2. True density measurement

The true density of particles was measured with an air pycnometer (Type 1000, Tokyoscience Co, Ltd.).

2.2.3. Measurement of Stokes density and Stokes diameter

The Stokes density (effective particle density for sedimentation) and the stokes diameter were determined by a settle meter method as previously reported (Vanderhasselt and Vanrolleghem,