European Journal of Pharmaceutical Sciences 65 (2014) 74–78

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Minimum rotation speed to prevent coning phenomena in compendium paddle dissolution apparatus

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ARTICLE INFO

Article history:
Received 26 June 2014
Received in revised form 4 September 2014
Accepted 8 September 2014
Available online 18 September 2014

Keywords:
Coning
Paddle
Dissolution
Particle size
Viscosity
Turbulence

ABSTRACT

The purpose of the present study was to investigate the applicability of the Zwietering equation to coning phenomena which often occur during dissolution testing. The minimum rotation speed at which coning phenomena disappeared (no coning rpm, NC_{rpm}) was experimentally determined for various particle and fluid properties in a compendium paddle apparatus with a round-bottom unbaffled vessel. The particle size, relative density and kinematic viscosity exponents in the Zwietering equation were optimized for NC_{rpm}. The particle size and relative density exponents were found to be similar with those for the general tank configurations of cylindrical flat-bottom baffled vessels. However, the kinematic viscosity exponent was significantly different. The equation obtained in this study showed sufficient accuracy (r^2 = 0.98, average error = 12 rpm) to estimate the occurrence of coning. The Zwietering equation was found to be applicable to the coning phenomena in the compendium paddle apparatus.

1. Introduction

The oral bioavailability of a drug depends on the dissolution profile of the drug product in the gastrointestinal tract. Several dissolution test apparatuses such as the paddle method, the rotating basket method, and the flow-through method, are listed in the pharmacopeia (Gray et al., 2009). The pharmacopeia paddle method, such as USP apparatus 2, is widely used in the pharmaceutical industry (Azarmi et al., 2007; Gray et al., 2009). The pharmacopeia paddle method employs a round-bottom unbaffled vessel and a single half-round paddle. However, this configuration often causes accumulation of particles near the bottom of the vessel due to insufficient agitation underneath the paddle (Bai and Armenante, 2008; Bai et al., 2007). This phenomenon is often referred as "coning" or "heap formation". Once the coning phenomena occurred, the dissolution rate of a drug could become slower and more variable compared to well-suspended cases (Gray et al., 2009). The occurrence of coning phenomena depends on the particle size, the particle density, the fluid viscosity, the fluid density, the apparatus configurations and the agitation strength. Some modifications of the compendium apparatus have been proposed to prevent the coning phenomena, for example, the PEAK™ vessel with a cone-shaped projection molded into the bottom of the vessel (Beckett et al., 1996; Mirza et al., 2005) and the crescent-shaped paddle (Qureshi, 2004a,b, 2006). However, little is known about the nature of the coning phenomena in the compendium apparatus. A better scientific understanding of the coning phenomena would be important for the Quality-by-Design approach (Lionberger et al., 2008; Yu, 2008; Zhang et al., 2011).

In the chemical engineering area, considerable attention has been devoted to the theoretical estimation of the minimum agitation speed (just-suspended speed, N_{js}) for particle suspension (Armenante et al., 1998). According to Zwietering (Zwietering, 1958), N_{js} is defined as the rotation speed at which no particles are visually observed to remain at rest on the vessel bottom for more than one or two seconds. For general paddle-tank configurations, N_{js} can be expressed by the Zwietering equation as (Zwietering, 1958),

$$N_{js} = a\left(\frac{D_{vessel}}{D_{paddle}}\right)^{b} \exp\left(c\frac{H_{paddle}}{D_{vessel}}\right)\frac{d_p^{l}}{D_{paddle}^{0.85}}\left(g\frac{\rho_p-\rho_f}{\rho_f}\right)^{m}\left(\frac{\mu_f}{\rho_f}\right)^{n}$$
$$= Ad_p^{l}\left(\frac{\rho_p-\rho_f}{\rho_f}\right)^{m}\left(\frac{\mu_f}{\rho_f}\right)^{n} \quad (1)$$

where D_{vessel} is the diameter of a vessel, D_{paddle} is the diameter of a paddle, H_{paddle} is the height of the paddle from the bottom, 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. As D_{vessel}, D_{paddle}, and H_{paddle} are fixed in the case of the compendium paddle method, these terms can be lumped together as a coefficient A. The Zwietering equation has been validated mainly for cylindrical flat-bottom baffled vessels

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http://dx.doi.org/10.1016/j.ejps.2014.09.010

with the Reynolds number of the paddle (Re: $N_{js}D^2_{paddle}\rho_f/\mu_f$) being >3000 (i.e., valid for turbulence flow) (Armenante et al., 1998; Zwietering, 1958). In this case, the exponent l, m, and n were reported to be 0.2, 0.45, and 0.1, respectively (Zwietering, 1958). However, the Zwietering equation has not been applied to the coning phenomena in the compendium paddle apparatus. The purpose of the present study was to investigate the applicability of the Zwietering equation to the coning phenomena in the compendium paddle apparatus and derive an equation to predict the occurrence of the coning phenomena from the particle properties, the fluid properties, and the rotation speed of the paddle.

2. Materials and methods

2.1. Materials

Cross-linked poly-(methyl methacrylate) microspheres (MBX series, MBX-8, MBX-12, MBX-20, MBX-30, MBX-40, MBX-50, MBX-60 and MBX-80) were provided by SEKISUI PLASTICS CO., Ltd (Osaka, Japan). Crystalline cellulose microspheres (CELPHERE®, CP-102, CP-203, CP-305 and CP-507 grades) were provided by Asahi Kasei Chemicals Corporation (Tokyo, Japan). Cellulose microspheres (CELLULOBEADS®, D-5, D-10, D-30, D-50, D-100 and D-200 grades) were provided by DAITO KASEI LTD (Osaka, Japan). Hydroxypropylmethylcellulose (HPMC) and methyl cellulose (MC) derivatives were provided by Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). As visual observation of the coning phenomena corresponds to that of the largest particles in the swarm of particles, the upper cut-off value of the particle size distribution should be sharp. The particle size distribution of CELPHERE® CP-102 was slightly diverse so that it was sieved by stainless sieves before use. The particle size distribution of the other particles showed a sharp upper cut-off value as received from the manufacturers. The scanning electron microscope images of these particles are shown in Fig. 1.

2.2. Methods

2.2.1. Determination of minimum rotation speed without coning formation

A compendium paddle dissolution test apparatus was used for this study (TOYAMA NTR-VS3PR (TOYAMA SANGYO CO., LTD.)). 900 mL of each fluid was de-gassed by sonication and maintained at 37 °C. The particles of 0.25 or 1 g were added to the vessel. In the case of MBX particles, the particles were wetted with a small amount of 0.1% tween 20 before adding to the vessel. After all particles were sediment on the bottom, the paddle speed was increased in a stepwise manner (each 5 or 10 rpm). The minimum rotation speed at which coning disappeared (no coning rotation speed, NC_{rpm}) was visually determined. More specifically, NC_{rpm} was defined as the rotation speed at which the particles covering the bottom of the vessel was occasionally removed within 5–10 s (Fig. 2). A similar definition was previously proposed for the analysis of the coning phenomena (Brucato et al., 2009). The viscosity of the fluid was varied by altering the concentration of HPMC or MC (<4%). The density of the fluid was varied by adding NaCl.

2.2.2. True density measurement

The true density of CELLUOBEADS® was measured by an air pycnometer (Type 1000, Tokyoscience Co, Ltd.). The true density values for the MBX series and CELPHERE® were obtained from the manufacturers.

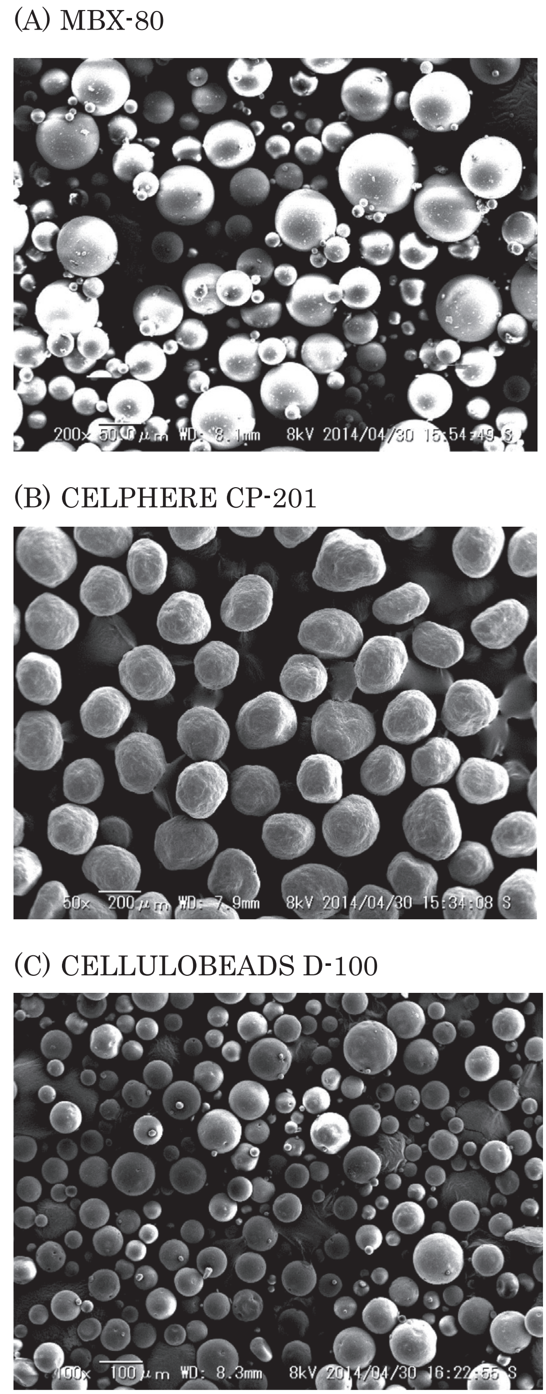

Fig. 1. Scanning electron microscope (SEM) images of particles. SEM: KEYENCE, VE-7800.

2.2.3. Measurement of effective particle density for sedimentation (Stokes density)

The Stokes densities of CELLUOBEADS® and CELPHERE® particles were determined from the terminal sedimentation velocity (v) and the size of the particles using the Stokes equation (Eq. (2)). A settle meter method (Vanderhasselt and Vanrolleghem, 2000; Vanrolleghem et al., 1996) was used to determine the v values. CELLUOBEADS® and CELPHERE® were wet-sieved before use (between the 90 and 100 μm meshes for CELLUOBEADS®, the 125 and 150 μm meshes for CELPHERE®). A small portion of particles were put in a 50 mL beaker (diameter: 4.7 cm) filled with a fluid. The fluid was then agitated using a long rectangle plate (width: