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Physical properties of pharmaceutical pellets

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HIGHLIGHTS

- We tested 14 samples of pharmaceutical pellets.
- Coefficient of restitution and friction, density, size, and hardness was evaluated.
- We used AFM for analysis of surface stiffness and roughness.
- Most pellets showed velocity dependent coefficient of restitution.

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ABSTRACT

A series of various methods were applied to characterize samples of pharmaceutical pellets. Fourteen pellet types were tested to obtain the coefficient of restitution, coefficient of friction, stiffness, flowability, and distribution of size, shape, and density. An atomic force microscope was used to determine the pellet surface properties. The values obtained for the coefficient of restitution ranged from 0.568 to 0.843, and a sample-specific dependence of impact velocity was demonstrated. Mean pellet size was between 807.2 and 1271 μm, granular density ranged between 1.086 and 1.483 g/ml, and the coefficient of friction was around 0.21 for pellet–steel contact and around 0.16 for pellet–glass contact. AFM provided information about surface stiffness and roughness; furthermore, the values obtained correlated well with the results of other methods. The values of Young's modulus of the pellets using the plate compression method or AFM surface testing were close to 1 GPa. The database of properties of commercially available sample pellets presented here represents a solid foundation for sound CFD and DEM simulations of pharmaceutical processes connected with the production of dosage forms comprising pellets.

1. Introduction

Pellets are spherical particles with a size normally between 100 and 1000 μm packed into capsules or compressed into tablets and taken orally. They are produced by an extrusion and spheronization process, by layering core pellets using drug dispersion, or by direct pelletization in a fluidized bed rotor chamber. Pellets are usually film-coated with one or more layers of polymer film that provide protection of the active ingredient or control the release of the drug (Fukumori and Ichikawa, 2006).

This study analyzed various properties of neutral pellets (microcrystalline cellulose and sugar) as well as various pellets that are available on the market as medicine. A broad range of commercial pellets was selected in order to assess the range of values of pellet properties. The data obtained will provide a better understanding of pellet properties and will also provide some basic parameters for models used in computer simulations of processes involving pellets. Computer simulations of pharmaceutical processes are more often used today due to the increase in computational capabilities (Kremer and Hancock, 2006). Many challenges still exist in the simulation of pharmaceutical processes, in particular detailed simulations of coating processes (Turton, 2008). In addition, this study is a valuable source of data useful for realistically setting parameters for CFD and DEM models for simulations of processes involving pellets as well as understanding the basic mechanical properties of pellets when designing a complex pharmaceutical form like a tablet comprising pellets.

Two kinds of computer simulations are normally used in modeling pharmaceutical processes. The first one is the discrete element method (DEM), in which each particle is modeled separately. It is used in simulations in many research fields dealing with granular materials (Zhu et al., 2008). DEM normally uses a spring-dashpot model to determine the force between particles and other models such as a simple Coulomb model for friction, capillary force models, and models for computing van der Waals forces (Zhu et al., 2007).

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One of the first DEM models used by Cundall and Starck was the linear spring dashpot model Eq. (1). It utilizes normal spring stiffness k_n and damping coefficient γ_n and has a constant coefficient of restitution (e) with regard to impact velocity Eq. (2).

$$F_n = -k_n\xi - \gamma_n\dot{\xi} \tag{1}$$

where F_n is the normal force, ξ is the overlap or displacement, and $\dot{\xi}$ is the velocity or displacement rate.

$$e = \exp\left(-\frac{\gamma_n}{2M}\pi\left(\frac{k_n}{M} - \left(\frac{\gamma_n}{2M}\right)^2\right)^{-1/2}\right) \tag{2}$$

where M is the mass of the particle.

Nonlinear models are normally Hertz-based, in which force correlates with overlap raised to the power of $\frac{3}{2}$. A general form of a Hertz-based DEM model was proposed by Kruggel-Emden et al. (2007):

$$F_n = -k_n\xi^{3/2} - \gamma_n\dot{\xi}\xi^{\tilde{\Theta}_n} \tag{3}$$

In the DEM model used by Kuwabara and Kono (1987), the value of the adjustable exponent $\tilde{\Theta}_n$ in Eq. (3) was 0.5, and in the model used by Tsuji et al. (1992) the value was 0.25. The value of 0.25 denotes the constant coefficient of restitution.

Walton and Braun's hysteric DEM model (Walton and Braun, 1986) uses two spring constants, one for loading (k_l) and the second for unloading (k_{ul}), and the coefficient of restitution describes the relation between the two

$$e = \sqrt{\frac{k_l}{k_{ul}}} \tag{4}$$

The second type of simulation also used in modeling some pharmaceutical processes is computational fluid dynamics (CFD), which can model each phase in the process as a fluid. Granular material can be modeled using granular models that are available for CFD, which consider the coefficient of restitution in the calculation of granular viscosities and solids pressure (van Wachem et al., 2001).

DEM-model parameters can be adjusted using the coefficient of restitution or contact time duration (Kruggel-Emden et al., 2007; Di Renzo and Di Maio, 2004; Stevens and Hrenya, 2005). Many measurements of the coefficient of restitution found in the literature were performed using metal spheres (Aryaei et al., 2010; Lorenz et al., 1997; Stevens and Hrenya, 2005; Weir and Tallon, 2005), ceramic spheres (Kharaz et al., 1999), glass spheres (Téllez-Medina et al., 2010), and calcium carbonate granules (Mangwandi et al., 2007). In any case, there is a lack of data obtained by using particles comprising pharmaceutical excipients (Bharadwaj et al., 2010).

The friction between particles influences their behavior during manufacturing and packaging as well, and is one of the basic input parameters in DEM simulations, expressed as the coefficient of friction and coefficient of rolling friction. Studies on the interparticle friction of pharmaceutical excipients on a nanoscale level were performed by Bunker et al. (2006) and with a powder/die friction approach during tableting by Cunningham et al. (2004). Other studies of friction were performed on tablets and capsules using a pin-on-disk tribometer (Hancock et al., 2010) and inclined plane to determine the coefficient of rolling friction (Ketterhagen et al., 2010).

Many studies have been conducted regarding pellet tensile strength because this property is an important factor in pellet tableting (Salako et al., 1998). Young's modulus is an important material property for most processes and it is an input parameter for DEM simulations using Hertz-based models. It has been determined for some pharmaceutical excipients (Bassam et al., 1990; Kachrimanis and Malamataris, 2004), some active pharmaceutical ingredients (Hancock et al., 2002), and some pellets (Bashaiwoldu et al., 2004). Poisson's ratio is also an important mechanical property and Roberts et al. (1994) have determined the value of microcrystalline cellulose and aspirin to be 0.3 and 0.29, respectively.

Selection of simulation parameters is first of all based on single-particle measurements; however, due to the complex nature of particles they are sometimes not sufficient. Bulk properties of granular material and simple experiments can provide data to fine-tune models and parameters in order to obtain more realistic behavior of simulated particles. These experiments can be simple, such as determination of mass flow (Anand et al., 2009; Persson et al., 2011), compression behavior of material (Frenning, 2008, 2010; Hassanpour and Ghadiri, 2004), or measurement of bulk density. Our experiments comprised mass flow, dynamic angle, and bulk density measurements.

Pellet size, shape, and density are the basic input parameters in both computer simulations; however, CFD can have only one particle size and density for one granular phase, whereas DEM simulation can easily model particles with various particle size and density. Both true and granular density were measured because they are useful in computer simulations, especially when considering drag force. Eventually, pellet size and shape can easily be determined using image analysis (Mozina et al., 2010; Podczeck et al., 1999).

In addition to basic single-particle and bulk experiments, we also performed surface-roughness and imaging analysis using atomic force microscopy (AFM). Our main motivating factor and goal was to identify differences between particles and to provide data for simulations. Evaluating the surface roughness of particles not only serves to predict physicochemical properties but also provides a reference to reflect any mechanical or physicochemical process involved in surface formation (Li and Park, 1998).

Final commercial pellets are normally composite materials. A pellet core might contain one or more layers of coating that can be either thin film polymer coating with a thickness of 10 μm or a layer containing an active ingredient from a few μm up to 100 μm. Due to this inhomogeneous structure, only the global mechanical property of pellets was determined in most tests.

2. Methods and materials

2.1. Materials

Microcrystalline cellulose-neutral pellets (Cellets 700, Harke Pharma, Germany) and neutral sugar spheres (Pharm-a-spheres, 710–850 μm, Hanns G. Werner GmbH, Germany) were used in the experiments. Cellets 700 pellets were sieved using 900 and 1000 μm analytical sieves to obtain narrow particle distribution. Alventa, Asasantin, Bazetham, Effectin, Lanzul S, Naklofen Duo, Olfen, Olicard, Ortanol S, Sporanox, Tanyz, and Teotard capsules filled with pellets were obtained from a local pharmacy. Glass spheres (1000–1200 μm, SiLibeads type GZ, Sigmund Linder, Germany) were used in some experiments for comparison.

2.2. Coefficient of restitution

The coefficient of restitution was calculated as the ratio of the impact velocity and the rebound velocity

$$e = -v_r/v_i \tag{5}$$

Pellets were released from five different heights using a nozzle connected to a vacuum system and the impact was recorded with a high-speed Casio Exilim EX-F1 camera equipped with a Raynox