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Research Paper

Mechanical particle coating using polymethacrylate nanoparticle agglomerates for the preparation of controlled release fine particles: The relationship between coating performance and the characteristics of various polymethacrylates

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ABSTRACT

We aimed to understand the factors controlling mechanical particle coating using polymethacrylate. The relationship between coating performance and the characteristics of polymethacrylate powders was investigated. First, theophylline crystals were treated using a mechanical powder processor to obtain theophylline spheres (< 100 μm). Second, five polymethacrylate latexes were powdered by spray freeze drying to produce colloidal agglomerates. Finally, mechanical particle coating was performed by mixing theophylline spheres and polymethacrylate agglomerates using the processor. The agglomerates were broken under mechanical stress to coat the spheres effectively. The coating performance of polymethacrylate agglomerates tended to increase as their pulverization progressed. Differences in the grindability of the agglomerates were attributed to differences in particle structure, resulting from consolidation between colloidal particles. High-grindability agglomerates exhibited higher pulverization as their glass transition temperature (T_g) increased and the further pulverization promoted coating. We therefore conclude that the minimization of polymethacrylate powder by pulverization is an important factor in mechanical particle coating using polymethacrylate with low deformability. Meanwhile, when product temperature during coating approaches T_g of polymer, polymethacrylate was soften to show high coating performance by plastic deformation. The effective coating by this mechanism may be accomplished by adjusting the temperature in the processor to the T_g.

1. Introduction

The coating process in pharmaceutical manufacturing is a unit operation to provide solid dosage forms with useful properties (such as controlled-release and moisture-resistant characteristics) that help enhance the stability and functionality of pharmaceutical products. Wet coating is the most common coating process in the pharmaceutical industry (Jones, 2008) and involves spraying a polymer solution or suspension onto granules or tablets in heated air using pan coaters or fluidized bed coaters. Dry coating processes are less common, but can decrease running costs by reducing the processing time and energy required for solvent evaporation, as well as minimizing environmental impact since no organic solvents are used. Dry coating methods include compression coating, hot-melt coating, supercritical fluid coating and dry powder coating (Bose and Bogner, 2007). In particular, dry powder coating has broad application in the pharmaceutical industry and various methodologies have been developed such as plasticizer-assisted coating, thermal-adhesion coating, and mechanical particle coating (Luo et al., 2008; Pfeffer et al., 2001; Sauer et al., 2007).

Coating techniques for fine particles have recently gained importance because small particles tend to distribute more evenly through the gastrointestinal tract than do large particles (Clarke et al., 1993; Davis et al., 1986; Meyer et al., 1988), and the controlled release of small particles would reduce the variation in bioavailability and the risk of toxicity caused by local high drug concentrations. Also, small coated pellets are required for the manufacture of orally disintegrating tablets with modified-release characteristics (Maeda et al., 2011; Mizumoto et al., 2008) as they offer a more pleasant feeling in the mouth (Kimura et al., 2015) and are less disrupted by tableting than large pellets (Ragnarsson et al., 1987). Moreover, coating techniques providing solid products less than 100 μm in diameter may be useful for the stabilization and functionalization of parenteral products (such as inhalational powders and suspensions for injection) (Jono et al., 2000). It is technically difficult to coat particles smaller than 100 μm using wet coating

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processes (Frey, 2016; Jono et al., 2000) as the core particles tend to agglomerate due to capillary action of the liquid droplets. Dry coating processes should be more suitable for coating fine particles. However, dry coating typically involves plasticizer-assisted coating and thermal-adhesion coating techniques that are more suited for large-size particulates (such as granules and tablets) rather than fine particles. The strong adhesion of liquid plasticizer or soft polymer induces agglomeration, again making the coating of core particles less than 100 μm in diameter technically difficult. In contrast, dry powder coating using a mechanical powder processor (called mechanical particle coating) is suitable for fine particle coating and is our technique of choice.

A mechanical powder processor (also known as a mechanofusion or hybridization machine) is an ultrahigh-shear mixer that can apply powerful impact, shear and compressive forces to sample powder. Mechanical stress is generated by the passage of powder through a narrow gap between the vessel wall and rotor blades, and centrifugal tumbling motion with swirling flow is generated using a high-speed rotor. Their combined action deagglomerates adhesive fine particles to promote the mixing of different materials. This process induces the arrangement and fixation of small guest particles onto large host particles, mainly through van der Waals forces, to form an ordered mixture of coated particles several microns in diameter without the use of solvent (Pfeffer et al., 2001), and mechanical particle coating is therefore suitable for the coating of fine particles. Furthermore, the coating can be achieved in a short time through a simple process that sample powder is mechanically treated with a high-speed rotor, thereby having advantages over the conventional coating techniques such as fluidized bed coating. Therefore, mechanical powder processors are used as a dry particle coater in the pharmaceutical, cosmetic and inorganic fields (Pfeffer et al., 2001) and additionally has the potential for scaling up treatment, as the processor equipped with a production-scale vessel has been already developed. In the pharmaceutical industry, mechanical particle coating is used to improve the flowability of cohesive powders (Yang et al., 2005; Zhou et al., 2010) and the aerodynamics of inhalational powders (Begat et al., 2009; Mujumdar et al., 2004). Improved powder characteristics are achieved by coating the host particles with a surface modification agent and this coating does not necessarily need to be uniform. Drug release is modulated by encapsulation rather than surface modification and the encapsulation film must be continuous, making the production of controlled-release particles through mechanical particle coating challenging. Nevertheless, sustained-release particles smaller than 100 μm can be prepared using this approach by using wax polymer (consisting of higher alcohol or fatty acid) as a coating material (Capece et al., 2015; Capece and Davé, 2014; Nakamura et al., 2016). Wax polymers have a low melting point and high deformability and thus spread easily over the surface of core particles to form a continuous film under mechanical stress. Deformable substances such as wax are required for mechanical particle coating of controlled-release particles, but it is difficult to construct diverse release profile products (such as zero-order release, pH-dependent release, and pulsatile release) using only wax. Cellulose derivatives and polymethacrylate are widely used as a coating material for controlled release in conventional coating processes such as wet coating and plasticizer-assisted coating (Miller and McGinity, 2008). Many derivatives with different water permeabilities and pH-dependent solubilities are manufactured, marketed, and used in the fabrication of sustained-release profile, site-specific release profile, or time-controlled release profile pharmaceuticals. However, cellulose- and methacrylate-based polymers cannot be used practically in mechanical particle coating because their deformability is lower than that of wax materials. Consequently, the application of mechanical particle coating to the manufacture of controlled-release particles is limited to the preparation of slow-release particles, although this approach is suitable for the coating of fine particles.

We are interested in expanding the application of mechanical particle coating in the pharmaceutical industry and previously reported a coating process using methacrylate polymer (Kondo et al., 2013). Composite particles were prepared as follows: (1) mechanical spheronization of theophylline (i.e., preparation of drug core particles), (2) powdering of polymethacrylate latex (i.e., preparation of coating powder), and (3) mechanical powder processing of theophylline spheres and polymethacrylate powder (i.e., mechanical particle coating). First, theophylline crystals with rod-like morphology were treated using a mechanical powder processor to produce theophylline spheres (with a size smaller than 100 μm) suitable for coating process. In general, drug core particles are prepared by layering inactive spherical particles with drug powder, but it is technically difficult to obtain small particles with high drug content in this approach, as particle size increased with increasing the amount of drug layering. Therefore, theophylline spheres were produced using the mechanical spheronization technique developed by the authors (Kondo et al., 2013, 2016) and used as core particles for mechanical particle coating. Second, polymethacrylate aqueous dispersion was powdered to produce polymethacrylate agglomerates. Since the size of coating polymer is suitable for being less than one tenth of the size of core particles, using submicron-sized polymer particles would be desirable for the coating of particles less than 100 μm. Thus, polymethacrylate latex composed of colloidal particles was powdered using two techniques involving freeze drying and spray freeze drying, and then used in mechanical particle coating experiments. Finally, mechanical particle coating was performed by mixing theophylline spheres and polymethacrylate agglomerates using the mechanical powder processor. The agglomerates obtained by spray freeze drying had a loose structure with numerous pores, making it possible to coat core particles effectively by the breakage of the agglomerates under mechanical stress. Meanwhile, the agglomerates obtained by conventional freeze drying had a tight structure without pores and showed ineffective coating due to insufficient destruction of the agglomerates. In conclusion, using the loose agglomerates, we succeeded in coating theophylline spheres less than 100 μm in diameter through mechanical particle coating using polymethacrylate and obtained controlled-release fine particles. However, because this investigation was done using one methacrylate polymer, the applicability of other polymethacrylates to the coating technique is not demonstrated. Also, the effect of polymer characteristics on the success or failure of coating is unclear. In the present study, to expand the application of the technique to the pharmaceutical industry, we aimed to understand the factors controlling mechanical particle coating using methacrylate polymer. We therefore examined coating effectiveness of five polymethacrylates with different characteristics to investigate the relationship between coating performance and the physical characteristics of polymers.

2. Materials and methods

2.1. Materials

Theophylline (TPL) (Wako Pure Chemical Industries Ltd., Osaka, Japan) was used as the model drug. Ethyl acrylate and methyl methacrylate copolymer (EUD-NE) dispersion (EUDRGIT NE30D, Evonik Japan Co. Ltd., Tokyo, Japan), ammonioalkyl methacrylate copolymer type B (EUD-RS) dispersion (EUDRAGIT RS30D, Evonik Japan Co. Ltd.), methyl acrylate, methyl methacrylate and methacrylic acid copolymer (EUD-FS) dispersion (EUDRAGIT FS30D, Evonik Japan Co. Ltd.), methacrylic acid copolymer LD (EUD-LD) dispersion (EUDRAGIT L30D55, Evonik) and methyl methacrylate and diethylaminoethyl methacrylate copolymer (Kol-SS) dispersion (Kollicoat Smartseal 30D, BASF Japan Ltd., Tokyo, Japan) were used as coating materials. All other chemicals and solvents were of analytical reagent grade.