

Dry Particle Coating with Polymeric Nanopowders for Fabricating Multi-Layered, Prolonged-Release Microparticles Using Theta-Composer[®]

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1. Introduction

A dry coating process for pharmaceutical preparations has gained much attention recently as an alternative to spray-coating processes because of its less heat-energy and short processing-time [1,2]. Constructing ordered mixtures of fine particles with coarse particles in dry state have been proposed in the hybridization [3] and mechano-fusion technologies [4]. These techniques have succeeded in producing the microparticles surface-modified with thin layers of very fine particles, and the nano-structured mixtures of nanoparticles under strong shearing stress. In pharmaceutical preparations, however, the controlled-release particulate systems require relatively thick, multi-layered structures of particles for constructing drug layer and diffusion barriers. Therefore, the present authors intended to use a high-speed elliptical-rotor type powder mixer (Theta-composer[®]) [5] which would apply milder force on powder particles than the hybridization and the mechano-fusion.

The objective of this study is to develop a dry particle coating technology using the Theta-composer[®] for the preparation of prolonged-release microparticles composed of core particles with multi-layer of binder, drug and polymeric coat.

2. Experimental Methods

Spherical microcrystalline cellulose particles (CP, Celphere 103, Asahi Chemical Ind., Japan) were employed as cores after sieved into 177-210 μm by an air-jet sieve (Alpine 200LS). Lauric acid (LA, mp. 44°C, 21.3 μm , Wako Chemical, Japan) pulverized by a hammer-mill was used as a binder. As a water soluble model drug, carbazochrome sodium sulfonate (CCSS, Sanwa Chemical, Japan) with yellowish color was used followed by ball-milled, and sieved into smaller than 63 μm .

Table 1. Materials and their particle sizes

Materials	Particle size (μm)
Microcrystalline cellulose	177-200
Model drug	5.4
Lauric acid	21.3

Mass median diameter of the drug powder thus obtained was 5.4 μm . Self-made acrylic polymer latexes composed of ethyl acrylate-methyl methacrylate and 2-hydroxyethyl methacrylate (poly(EA-MMA-HEMA), monomer molar ratio=6:12:9, $T_g=77^\circ\text{C}$) were synthesized by emulsion polymerization as previously reported [1]. The mean hydrodynamic diameter of the latex particles was 95 nm when measured at 25°C using a Horiba LB-500 dynamic light scattering particle size analyzer. The poly(EA/MMA/HEMA) latexes thus synthesized were freeze-dried with or without pre-salting-out treatment to achieve two different types of nano-powders as a coating material for prolonged-release of the drug.

Dry particle coating was carried out using the high-speed elliptical-rotor type powder mixer (Theta-composer[®], Tokujin Corporation, Japan). The effective vessel volume was 111 mL and the clearance between the rotor and vessel was 1 mm. Three grams of the pulverized LA were first layered onto 25 g of CP. Next, 3 g of a micronized CCSS was layered on the LA-layered core-particles and subsequently coated with nanopowders prepared by freeze-drying of the poly(EA/MMA/HEMA) latexes with (P/FD) or without (FD) pre-salting-out treatment. The nanopowder coating was repeated four times with the typical feed amount of 3 g in each coating step.

3. Results and Discussion

Under the operating conditions (Fig. 1) with the stepwise addition of small amounts of fine powders and the stepwise elevation of the rotational speed of the rotor to attain the ordered mixing at 500-2000 rpm and the fine particle fixing by melted LA at 2000-3000 rpm, the CCSS-layered particles could be obtained at the yield of 92% without any agglomeration.

The coating yields of nanopowders were found to be varied depending on their particle morphology. The coating yield of FD (a flake-like particle morphology composed of highly fused primary latex particles) was 75% at the first coating step, but decreased to around 15% at the subsequent steps. In contrast, P/FD (free-flowable, porous particles composed of loosely agglomerated

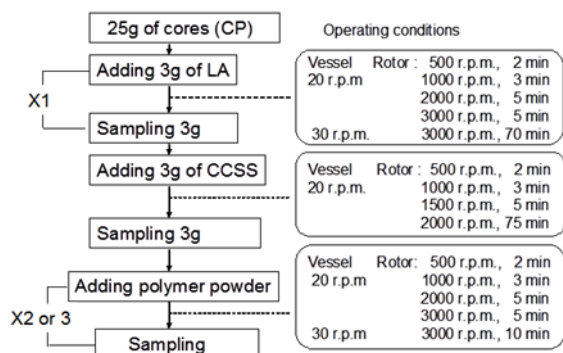


Fig. 1. Operating conditions in dry-coating

latex particles) always showed high coating yields around 90% through the whole coating steps, indicating that morphology of nanopowders was an important factor governing their coating efficiency.

As indicated in Fig. 2, the microparticles obtained by the coating of P/FD nanopowders and the post-thermal curing at 60°C for 12h exhibited a prolonged release of CCSS in purified water. The cumulative amounts of CCSS in the microparticles coated with 36 wt% of P/FD nanopowders were 55% at 8h and 98% at 24h. The release rate was controllable by changing the feed amount of P/FD nanopowders.

4. Conclusion

The results of the present study demonstrated that the use of well-designed polymeric nanopowders was effective for dry coating process using the Theta-composer, leading to successful preparation of multi-layered microparticles releasing the water-soluble drug over 24h.

5. Acknowledgements

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6. References

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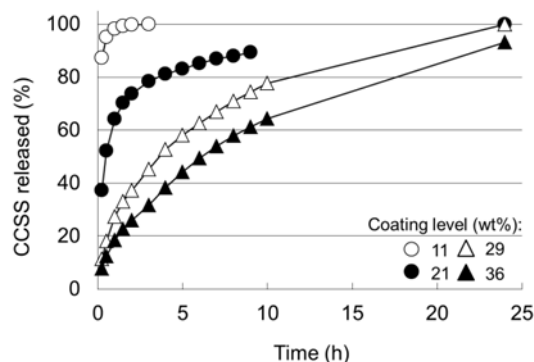


Fig. 2. CCSS release from microparticles coated with P/FD in purified water

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