# NOVEL PREPARATION OF FREE FLOWING SPHERICALLY GRANULATED DIBASIC CALCIUM PHOSPHATE ANHYDROUS FOR DIRECT TABLETTING

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Free flowing spherically granulated (average diameter, 70 or 115 $\mu$m) dibasic calcium phosphate anhydrous (DCPA) for direct tabletting was prepared by a restricted crystal growing synthesis of DCPA, followed by spray drying of its aqueous dispersions. The spherically granulated DCPA had larger specific surface area (32 to 34 $m^2/g$), because they had porous structures composed of very fine primary crystals (Heywood diameter, 0.1 − 1.0 $\mu$ m) compared to conventionally prepared DCPA (Heywood diameter, 2.0−5.0 $\mu$m). The crystallinity of granulated DCPA was lower than that of conventional DCPA. Those micromeritic characteristics of granulated DCPA might correlate closely with their dramatically improved tablettability.

KEY WORDS dibasic calcium phosphate anhydrous; restricted crystal growing synthesis; spray drying; flowability; compressibility; direct tabletting

Dibasic calcium phosphate anhydrous (DCPA) has been widely used as an excipient for direct tabletting, because of properties such as higher bulk density, lower hygroscopicity and neutral pH of its aqueous dispersions.[1] The DCPA is conventionally synthesized as fine crystalline forms from phosphoric acid and calcium oxide in aqueous suspension. The precipitated DCPAs are coarse plate-like crystals, having poorer compressibility and flowability than cellulose derivatives, such as microcrystalline cellulose.

The aim of present study is to develop a novel DCPA having greatly improved compressibility and flowability compared with conventional DCPA. This was successfully accomplished by employing a restricted crystal growing synthesis to reduce crystal size of the product[2] and spherical granulation of the products by spray drying.[3, 4] In this paper, the novel preparation process of spherically granulated DCPA (SGDCPA) and their improved characteristics for direct tabletting are described.

Three hundred thirty gms of calcium oxide (analytical chemical grade, Wako) were dispersed in 2000 ml of distilled water, then agitated for 30 min to make milk of lime; the resultant aqueous dispersions were sieved through a 100 mesh (opening diameter, 150 $\mu$m) sieve to remove coarse particles. The milk of lime was diluted to 7.1% concentration on a calcium base by adding water to the system. Citric acid (15.8 g, analytical chemical grade, Wako) equivalent to 5 mol% of the theoretical yield of DCPA was dissolved in 2000 ml of distilled water. The milk of lime aqueous dispersions (1100 ml) and 294 g of 50 % aqueous solution of phosphoric acid (analytical chemical grade, Wako) were concurrently fed into the citric acid solution at 73 ml/min maintaining pH 4−5, and agitated for 30 min under ambient temperature for the reaction to produce dibasic calcium phosphate dihydrate. Introduction of citric acid to the system was a key point to precipitate fine crystals by means of the competitive reaction of calcium ion with phosphoric acid and citric acid having coordinating capacity. The reaction slurries were agitated for 2 hr at 70−100 °C to transform dibasic calcium phosphate dihydrate to DCPA. The residual citric acid in the precipitates was thoroughly removed by washing with distilled water, and drained under a reduced pressure. The drained crystals of 5 runs were diluted to 20% of aqueous dispersions, which were directly spray dried at 300 °C (inlet temperature) to 200 °C (outlet temperature) using a spray dryer (S-50N/R, Niro, Denmark) with a nozzle (pressure, 20 − 30 $kg/cm^2$) or rotary disk (rotating speed, 8000 − 10000 rpm) for atomization. The spray dried products with the nozzle and the rotary disk were termed SGDCPA-SG and -S, respectively.

Scanning electron microphotographs (taken with a JSM-T200, JEOL) of DCPAs are shown in Fig. 1.

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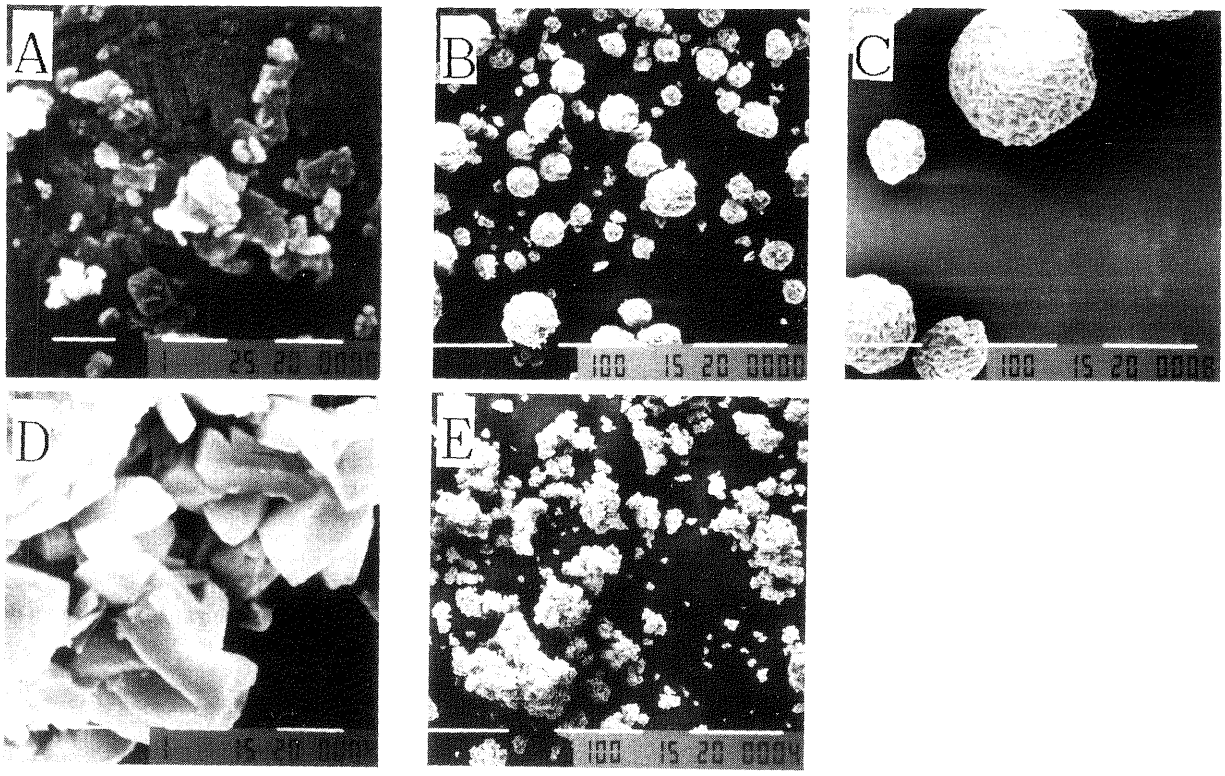


Fig. 1. Scanning Electron Microphotographs of DCPAs
A, SGDCPA primary crystals, scale, 1 $\mu$m;
B, SGDCPA-S, scale, 100 $\mu$m; C, SGDCPA-SG, scale, 100 $\mu$m;
D, Conventional DCPA primary crystals, scale, 1 $\mu$m;
E, Conventional DCPA, scale, 100 $\mu$m.

Conventional DCPAs are aggregated powder composed with plate-like crystals having Heywood diameter of 2.0—5.0 $\mu$m, measured by a photographic counting technique. The SGDCPAs are spherically granulated forms consisting of fine primary crystals (Heywood diameter, 0.1—1.0 $\mu$m). X ray diffraction patterns (diffractometer, X'Pert PW3040, Philips, Holland) of DCPAs in Fig.2 proved that the crystallinities of SGDCPAs were reduced compared with that of conventional DCPA. The crystallinities of SGDCPAs did not change even after aging at 40 ℃ and 75 % relative humidity (R.H.) for 6 months. The micromeritic properties of DCPAs are tabulated in Table 1. The data are the mean value of three different batches, and the standard deviations are listed in the table. The SGDCPAs were free flowing powder, although having rather higher specific volumes. This was proved by their lower repose angles than that of conventional DCPA, cohesive powder. The SGDCPAs have higher oil and water adsorption capacities because of their larger specific surface areas due to the more porous structure than that of conventional DCPA. The tablets of DCPAs were prepared by compressing 400 mg of the powder using a static oilpress (Brinell hardness tester, Yonekura) with flat-type punches and die (diameter, 12 mm), which were lubricated with about 0.5 % of magnesium stearate (Lot No. 20306M, Nippon Yushi) at each run. The hardness -- measured by a Monsanto hardness tester (Kayagaki) -- of the tablet with the SGDCPA was dramatically increased under compression pressure, as shown in Fig. 3, over the tablet of conventional DCPA showed lower compressibility. These findings were also confirmed in terms of the greater tensile strengths (T) of the tablets with SGDCPA-SG (i.e., 23.8 to 59.8 kg/cm$^2$) and SGDCPA-S (i.e., 25.5 to 57.2 kg/cm$^2$) required for destruction than those of conventional DCPA (i.e., 2.0 to 5.2 kg/cm$^2$).

$$T = 2F/\pi DL$$

where F is tablet hardness, D and L are diameter and thickness of tablet. No change in the tablet hardness was found even after storage under 40 ℃ and 75 % R.H. for 6 months. The disintegration times (> 30 min)

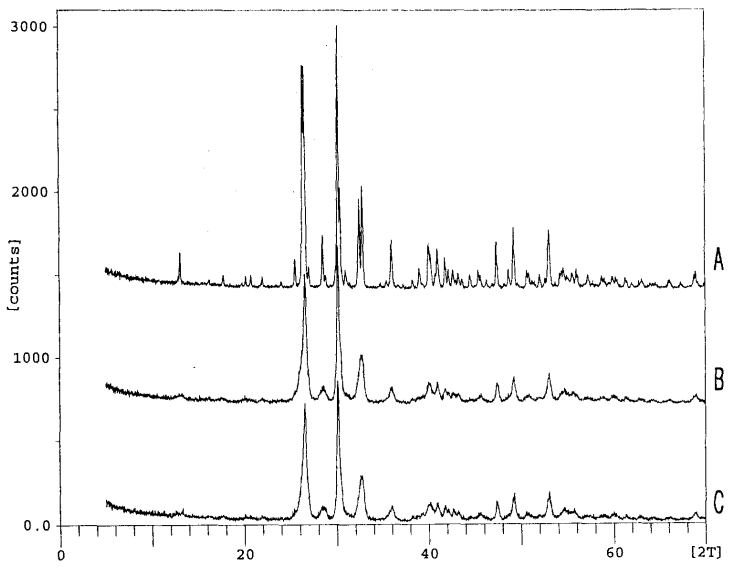


Fig. 2. X Ray Diffraction Patterns of DCPAs
A, Conventional DCPA; B, SGDCPA-S; C, SGDCPA-SG.

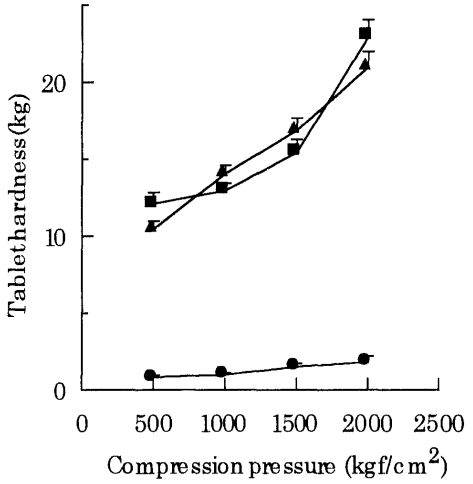


Fig. 3. Relationship between Compression Pressure and Tablet Hardness
Each point represents the mean value ± S.D. (n=10). ■, SGDCPA-SG; ▲, SGDCPA-S; ●, Conventional DCPA.

Table 1. Micromeritic Properties of DCPAs

| | SGDCPA | | Conventional |
|---|---|---|---|
| | -SG | -S | DCPA |
| Specific volume (ml/g) | | | |
| Loosely packed volume | 2.3±0.1 | 2.3±0.1 | 1.3±0.1 |
| Closely packed volume | 2.0±0.2 | 1.8±0.1 | 0.9±0.0 |
| Mean particle size ($\mu$m) | 113±2.7*1) | 68±2.5*1) | 43±3.5*2) |
| Repose angle (°) | 31±0.6 | 35±0.6 | 42±0.6 |
| BET specific surface area*3) (m$^2$/g) | 33.68±1.99 | 34.30±1.32 | 1.95±0.0.52 |
| Mean pore size*3) (Å) | 73.54±7.87 | 46.00±9.71 | —*4) |
| Oil adsorption capacity*5) (ml/g) | 0.81±0.08 | 0.91±0.04 | 0.15±0.02 |
| Water adsorption capacity*5) (ml/g) | 0.81±0.02 | 0.67±0.06 | 0.13±0.02 |

*1) Sieving method (ES-65, Iida Seisakusho) *2) LASER method (SALD-2000, Shimadzu)
*3) Porosimeter (GEMINI2360, Shimadzu) *4) Not detected *5) measured by JIS K5101

of SGDCPA tablets in aqueous medium were measured by the disintegration test method specified in J.P. The disintegration rates decreased with increased tablet hardness. However, they were much improved (i.e., 0.5 min) by formulating a disintegrant, e.g. 5 % of carmellose calcium, in the tablet.

In conclusion, spherically granulated DCPA prepared by the present new technique with restricted crystal growing synthesis and spray drying granulation remarkably improved the flowability and compressibility of DCPA for direct tabletting. The free flowing properties of SGDCPA were mainly caused by a significant reduction in interparticle friction (lower repose angle) due to their spherical shape. Plastic deformation of SGDCPA, having porous structure and lower crystallinity, during compression might be responsible for increasing the interparticle bonding in the tablet (higher tensile strength). [5]

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