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Original Article

Dicalcium Phosphate Blended with Native or Agglomerated Tapioca Starch for the Production of Directly Compressed Tablets

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Rapee Jarungsirawat[1] and Thaned Pongjanyakul[1]

Abstract

The objective of this work was to investigate the characteristics of powders and tablets prepared from blends of dicalcium phosphate dihydrate (DCPD) with native tapioca starch (TS) or agglomerated tapioca starch (AGTS) at various ratios. The results showed that DCPD had a Carr's index of 4.92%, whereas AGTS and TS were 14.70% and 27.45%, respectively. Moreover, the repose angle of TS (39.04°) was higher than that of DCPD (32.17°) and AGTS (32.40°), resulting in reduced blend flowability as TS content increased. Higher TS or AGTS ratios in the blends resulted in decreased yield pressure and increased yield strength compared with DCPD, as indicated by the Heckel and Kawakita plots, thereby enhancing plastic deformation under compression. TS tablets were harder than DCPD tablets at 62.4 and 124.9 MPa. However, the trend reversed at higher pressures. In contrast, the hardness of AGTS tablets was consistently higher than that of DCPD tablets. Additionally, the DCPD-AGTS blends produced propranolol hydrochloride (PPN) tablets with higher hardness than the DCPD-TS blends. The DCPD tablets with PPN showed the longest disintegration time (>45 min), whereas those of the TS and AGTS tablets with PPN had disintegration times of 1.09 and 6.22 min, respectively. Thus, the addition of TS or AGTS improved the tablet disintegration. Moreover, the PPN dissolution from the DCPD tablets was enhanced by the incorporation of TS or AGTS, particularly at the 0.5:0.5 DCPD:TS/AGTS ratio. Overall, AGTS can modify the properties of DCPD tablets compared to TS. The DCPD-AGTS blends show promising performance for producing immediate-release tablets.

Keywords

Dicalcium phosphate, tapioca starch, agglomeration, compressibility, flowability, direct compression

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Introduction

The direct compression method is a simple, cost-effective, and time-efficient process for producing tablet dosages.[1,2] In this method, a compression pressure is applied to a mixture of powders that includes the active pharmaceutical ingredient, a diluent, and other excipients, resulting in a cylindrical compact.[3] This approach is popular for tablet production because its steps are relatively straightforward compared to those of other methods.[4] However, it is essential to choose a diluent with good flowability and compressibility in the formulation.[5–7] Diluents used in this method can be classified into two categories: Inorganic, such as dicalcium phosphate (DCP), and organic materials, such as cellulose and starch.[3,8] Additionally, blends of inorganic and organic materials are often used to modify tablet physical properties and enhance product performance.

DCP, in the form of dicalcium phosphate dihydrate (DCPD), is an inorganic, insoluble diluent commonly used

[1] Division of Pharmaceutical Technology, Khon Kaen University, Khon Kaen, Thailand

Corresponding author:
Thaned Pongjanyakul, Division of Pharmaceutical Technology, Khon Kaen University, Khon Kaen 40002, Thailand.
E-mail: thaned@kku.ac.th

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in the production of tablets and capsules.[3] DCPD appears as a white, odorless, tasteless powder with low hygroscopicity, and it can form monoclinic crystals.[9] Its particles are rough and irregularly shaped.[10] DCPD in the unmilled form exhibits good flowability, making it a suitable excipient for direct compression. However, it also has a drawback: It possesses poor compressibility.[11] To improve the compressibility of DCPD, blends with materials that exhibit plastic deformation under compression have been studied.[3] Combining DCPD with microcrystalline cellulose in an appropriate ratio can enhance compression characteristics.[10,12–14]

Tapioca starch (TS), derived from the root of cassava (*Manihot esculenta* (L.) Crantz) in the Euphorbiaceae family,[15] is a valuable option in pharmaceuticals due to its transparent paste, bland flavor, and low levels of lipids and protein.[16] It can serve various functions, including as a diluent, binder, and disintegrant in solid dosage forms.[17] However, the use of TS as a primary diluent in direct compression tablets is limited due to its inadequate flowability and compressibility.[16] To improve these properties, the agglomeration technique has been used. Agglomeration is a size enlargement method by which fine particulates can be created into larger particles by mechanical agitation in the presence of a liquid phase. A simple method of particle agglomeration can be achieved by wet granulation using a polymer binder dispersion.[18] TS can be agglomerated with agents such as sodium alginate[19] and polyvinylpyrrolidone (PVP).[20] The agglomerating agents, dispersed or dissolved in water, could induce liquid bridges and capillary forces between particles, resulting in the densification of particle groups during mixing. Then, the liquid bridges could be converted into solid bridges upon drying. Thus, the agglomerating agents act as interparticle bridges, enabling them to adhere to one another and form larger agglomerates.[21–24] This results in enhanced flowability. Additionally, these agents promote cold-welding, which forms chemical bonds or solid bridges on the particle surfaces,[25] and plastic deformation under compression pressure. Consequently, agglomerated tapioca starch (AGTS) demonstrates improved flowability and compressibility, making it suitable as a diluent for directly compressible tablets.[19,20,26]

Based on the literature, AGTS has the potential to modulate the characteristics of DCPD in powder and tablet forms. Blends of DCPD and AGTS may function as a novel inorganic-organic (hybrid) diluent for tablet production via direct compression. AGTS, prepared with 4% PVP as an agglomerating agent, was employed in this study because the resulting AGTS exhibited acceptable particle strength and flowability. In addition, this AGTS gave sufficient hardness after compression.[20] Moreover, the characteristics of the DCPD-TS blends were also investigated and compared with those of the DCPD-AGTS blends to prove the superiority of this hybrid diluent in this study.

This study aimed to investigate the flow and compression properties of DCPD-AGTS and DCPD-TS blends prepared by simple mixing at various mixing ratios. The deformation behavior of these blends under compression was analyzed using the Heckel and Kawakita plots. The relationship between tablet thickness or hardness and compression pressure was examined in non-drug tablets to eliminate interference from drug particles in diluent bonding. The blends were also evaluated as diluents in propranolol hydrochloride (PPN) tablet formulations to assess their physical properties, disintegration time, and drug dissolution. Water-soluble PPN was used as the model drug in this study. PPN powder presented low flowability and poor compressibility, as the pure PPN tablets had broken edges after compression.[19] Thus, this powdered drug can be used to test a tablet diluent intended for direct compression.

Materials and Methods

Materials

DCPD in granular form was purchased from Reephos Food Ingredients Co., Ltd (Jiangsu, China). Of this, 87% by weight of DCPD had particles larger than 150 microns. TS was obtained from Kaensiri Starch Co., Ltd (Khon Kaen, Thailand). PPN and PVP K30 were obtained from Changzhou Yabang Pharmaceutical Co., Ltd. (Changzhou, Jiangsu, China) and Union Sciences Trading Co., Ltd. (Khon Kaen, Thailand). Magnesium stearate was purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). All other materials were used as received.

Preparation of AGTS with 4% PVP

AGTS with 4% PVP was prepared using the method reported in the previous study.[20] PVP (8 g) was dispersed in 90 mL of distilled water to achieve a clear dispersion. This dispersion was gradually added to and blended with 192 g of TS in a mortar and pestle until a damp mass was formed. The damp mass was passed through a 1.7-mm sieve and dried at 50 ºC in a hot air oven. Next, the dried particles were passed through a 150-µm sieve (mesh No. 100). For particle size selection, the AGTS retained on a 75-µm sieve (mesh No. 200) was collected for use in this study. The particle size of the AGTS obtained was measured as described under 'Particle Size Analysis of TS, AGTS, and DCPD. The AGTS was stored at room temperature (26 °C–28 °C) in a desiccator filled with silica gel beads before investigation.

Particle Size Analysis of TS, AGTS, and DCPD

The particle sizes of TS, AGTS, and DCPD were measured using a laser diffraction analyzer equipped with a dry sample dispersion unit (Mastersizer 2000 Model Scirocco 2000, Malvern Instrument Ltd., UK). Samples (6 g) were placed in a

general-purpose tray and analyzed under an air pressure of 0.12 MPa with a feed rate of 50%–55%. Obscuration values ranged from 2% to 4%. For each sample, three scans were performed, and particle size was reported as the volume-weighted mean diameter, *D*(4,3). The polydispersity index (span) was calculated as (*D*90-*D*10)/*D*50, where *D*10, *D*50, and *D*90 represent the volume-based particle size percentiles, indicating the percentage of particles smaller than that size.[26]

Preparation of DCPD-TS and DCPD-AGTS Blends

In this study, DCPD-TS and DCPD-AGTS blends were prepared at five weight ratios: 100:0, 75:25, 50:50, 25:75, and 0:100. These blends were prepared by weighing each component and mixing them using the geometric dilution method in a roto-mixer for 5 min before investigation.

Characterization of DCPD-TS and DCPD-AGTS Blends

Densities and Particle Flowability

Bulk density (Db) is the ratio of the mass of an untapped powder sample to its volume, expressed as g/mL. A powder sample (15 g) was poured into a 50 mL cylinder by obliquely filling the cylinder at approximately 45°. After that, the powder sample volume was measured, and the Db was calculated. The cylinder containing the powder sample was then tapped from a height of 1.5 in. until the powder volume remained constant. The final volume was recorded to compute the tapped density (Dt). For particle flowability of the samples, Carr's index and angle of repose were assessed. Carr's index was related to the bulk and tapped densities and could be calculated using the formula: Carr's index (%) = 100 × (Dt-Db)/Dt.[16,27,28] For the angle of repose, the powder sample was gradually poured through a glass funnel onto a flat surface at a consistent height. The height (h) and radius (r) of the resulting pile were measured,[16,28] and the angle of repose (θ) was calculated using the formula:[29]

$$\theta = \tan^{-1}\left(\frac{h}{r}\right) \tag{1}$$

The true density of the powder sample was determined using a liquid-displacement method with a 5-mL pycnometer (Leaz®, Wertheim, Germany), using acetone as the liquid to prevent the granules' ingredients from dissolving. A weighed pycnometer was filled with 1 g of the granules and weighed accurately. Acetone was then added to fill the pycnometer containing the granules to the maximum volume, and the total weight of the filled pycnometer was recorded. The weight of the acetone in the pycnometer without the sample was also determined. The true density was calculated using the following equation:[30]

$$\text{True density} = \frac{W_A \times W_G}{5\left(W_A - W_{GA} + W_G\right)} \tag{2}$$

where W_A, W_G, and W_{GA} represent the weights of acetone, granules, and granule-acetone mixture in the pycnometer, respectively.

Compressibility

The Heckel analysis describes the compression behavior of a material in terms of its relative density under applied compression pressure. The foundation of the Heckel plot for powder compression is that the densification of the bulk powder under pressure follows first-order kinetics. This relationship is expressed by the following equation:[31]

$$\ln\frac{1}{1-D} = KP + A \tag{3}$$

where D represents the relative density of the tablet (the ratio of tablet density to the true density of the sample) under compression pressure (P). K is the slope of the linear portion of the Heckel plot, and the reciprocal of K provides the mean yield pressure (P_y). The A value describes the densification of the samples due to initial particle rearrangement (Da), which can be calculated using an additional equation:

$$D_a = 1 - e^{-A} \tag{4}$$

The samples were compressed into tablets at various compression pressures, using a hydraulic press (Retsch™ PP 25 Pellet Press, Haan, Germany) with applied pressures ranging from 31.2 to 249.8 MPa. A 10 mm-diameter flat-faced die and punch, which had been lubricated using magnesium stearate powder, were used. For each compression pressure, three 400-mg tablets were compressed. The out-die thickness of each tablet was measured immediately after ejection using a digital Vernier caliper with an accuracy of ±0.01 mm. The tablet density under compression pressure was calculated, and the relative density of the tablets (D) was also computed. Subsequently, the relationship between ln[1/(1 − D)] and P was plotted, and the slope and intercept were determined.[31–33]

The Kawakita analysis is used to investigate particle deformation under compression pressure by examining the relationship between compression pressure and powder volume change. The Kawakita equation was presented as follows:[32,33]

$$\frac{P}{C} = \left[\frac{P}{a} + \frac{1}{ab}\right] \tag{5}$$

$$C = \left[\frac{\left(V_0 - V\right)}{V_0}\right] \tag{6}$$

where P is the compression pressure, and C describes the volume decrease after applying compression pressure. V_0 is the initial volume of the powder filled into the die, which was

computed from the Db. V is the tablet volume after compression, determined from tablet thickness. The a value shows the initial porosity, which decreases when pressure is applied. The b value is proposed to be inversely related to the yield strength of particles (P_k). Data for P/C and P were plotted, and the slope ($1/a$) and intercept ($1/ab$) constants were obtained.

SEM with EDX Analysis

The particle morphology of TS, AGTS, and DCPD was examined using scanning electron microscopy (SEM). The powders were applied to a metallic stub with carbon adhesive tape and subsequently coated with gold. The samples were then analyzed using a Hitachi SU3800 scanning electron microscope (Tokyo, Japan). In addition, the surface morphology and internal structure of the tablets were characterized using SEM and energy-dispersive X-ray (EDX). The tablets or their cross-sections were placed onto stubs with carbon adhesive tapes and coated with gold before analysis with the Hitachi S-3000N scanning electron microscope. To evaluate the surface chemical composition, an EDX analyzer (AZtecLiveOne with Xplore 30, Oxford Instruments, England) was utilized, along with AZtec® 5.0 SP1 software. The accelerating voltages for SEM and EDX were set at 5 kV and 20 kV, respectively.

Preparation of Tablets Without or With a Drug

TS, AGTS, DCPD, DCPD-TS, and DCPD-AGTS blends were compressed at various compression pressures. The 396 mg diluent and 4 mg of magnesium stearate were mixed using a roto-mixer for 5 min. The final mixtures (400 mg) were filled into a 10 mm-diameter flat-faced die and punch and compressed into a tablet using a hydraulic press at 62.4, 124.9, and 249.8 MPa without holding time (Retsch™ PP 25 Pellet Press, Haan, Germany). These tablets were evaluated for thickness and hardness, and the relationship between compression pressure and tablet thickness/hardness was plotted.

In this study, the drug-loaded tablets contained 40 mg of PPN (10% w/w) and were mixed with 356 mg of diluent (89% w/w) using the geometric dilution technique for approximately 5 min. Then, 4 mg of magnesium stearate (1% w/w) was added to the mixture and mixed again for 5 min. The final mixture (400 mg) was weighed and filled into a 10 mm-diameter flat-faced die and punch. The PPN tablets were compressed at 249.8 MPa using a hydraulic tablet compression machine without holding time. The PPN tablets were obtained and stored in a silica gel bead desiccator at room temperature before evaluation.

Evaluations of Tablets

Thickness and Hardness

The thickness of the tablets was determined using a digital caliper (Kennedy DCS150, Leicester, England), whereas tablet hardness was measured using a hardness tester (VanKel VK200, Cary, NC, USA). Five tablets were measured, and the mean and standard deviation were calculated.

Disintegration Time

A basket rack assembly disintegration test apparatus equipped with a cover sieve (Erweka ZT-324, Langen, Germany) was used to evaluate the tablet's disintegration time. The medium used was 0.1 N HCl at 37.0 °C ± 1.0 °C. Each tablet was placed into the basket without a disc. The disintegration time was recorded when the tablet was entirely disintegrated, and no residual fragments remained on the basket screen.

Drug Dissolution

The paddle method of the USP dissolution apparatus (VanKel VK7000, Cary, NC, USA) was used to evaluate the dissolution profile of PPN tablets. The dissolution medium used was 750 mL of 0.1 N HCl, with the temperature maintained at 37.0 °C ± 1.0 °C. At each specified time point, the samples were collected and replaced with a fresh volume of medium. Then, the PPN concentration was analyzed by a UV-visible spectrophotometer at 289 nm. The time to achieve 50% drug dissolution ($T_{50\%}$) was calculated.

Statistical Analysis

The statistical differences in hardness, disintegration time, and $T_{50\%}$ values of the tablets, with at least three replications, were analyzed using one-way analysis of variance with Tukey's honest significant difference test for multiple comparisons and Student's t test for two-sample comparisons. All statistical investigations were done using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY). Statistical significance of all differences was set at $p < .05$.

Results and Discussion

Particle Size and Morphology of Materials

SEM pictures and particle sizes of TS, AGTS, and DCPD are presented in Figure 1 and Table 1. The granules of TS were oval, truncated, and rounded in shape. The particle size (D[4,3]) of TS granules was 42.92 ± 0.05 μm, with a wide distribution (span = 1.67). They showed both independent and aggregated particles. SEM images of AGTS showed that particle enlargement of TS could be achieved by adding PVP as an agglomerating agent. The particle size of AGTS was 134.98 ± 0.35 μm, with a span value less than unity, indicating a narrow particle size distribution. The particle size of DCPD was 276.79 ± 2.86 μm, with a span value of 0.79. The DCPD particles showed a rough, irregular surface, tightly fused crystals, and irregularly shaped particles. Among these materials, DCPD had the largest particles, whereas TS had the smallest.

Density and Flowability of the DCPD-starch Blends

Table 2 shows densities and flowabilities of DCPD, TS, AGTS, and blends. DCPD had the highest bulk, tapped, and true densities. The Db of AGTS was greater than that of TS due to its larger particle size, whereas TS showed higher tapped and true densities than AGTS. The rank order of densities of the three materials was true density > Dt > Db because the true density is the density of the actual solid material with minimal void space between particles. For DCPD-TS and DCPD-AGTS blends, all densities increased with increasing DCPD ratio. However, the DCPD-TS (0.75:0.25) blend had bulk and tapped densities similar to those of DCPD, suggesting that the addition of TS at this ratio did not affect the bulk properties of DCPD powder. This may be due to interparticle interactions between TS and DCPD at this ratio.

The bulk and tapped densities were used to compute Carr's index (Table 2). DCPD showed the lowest Carr's index, indicative of excellent flowability, whereas TS's Carr's index was 27.45%, suggesting a passable level of flowability. Increasing the particle size of AGTS via agglomeration reduced the Carr's index to 14.70% and provided good flowability. Similar results were observed when measuring the repose angle (Table 2). The DCPD (repose angle = 32.17°) and AGTS (repose angle = 32.40°) presented good flowability, whereas fair flowability was obtained from TS (repose angle = 39.04°). The Carr's index represented the friction and cohesiveness of powders under static conditions.[34] In contrast, the angle of repose can be used to assess the dynamic friction characteristics of powders.[35] In this study, AGTS showed better flowability than TS because particle enlargement reduced cohesiveness and dynamic friction. However, DCPD showed the lowest cohesiveness under static conditions, as indicated by Carr's index. For the DCPD-TS blends, increasing the TS ratio led to higher Carr's index and repose angle, indicating lower flowability than DCPD. In contrast, the DCPD-AGTS blends gave Carr's indices less than 10 and repose angles in the range of 32.7°–33.7°. This result suggested that the DCPD-AGTS blends had good to excellent flowability and exhibited similar dynamic friction characteristics.

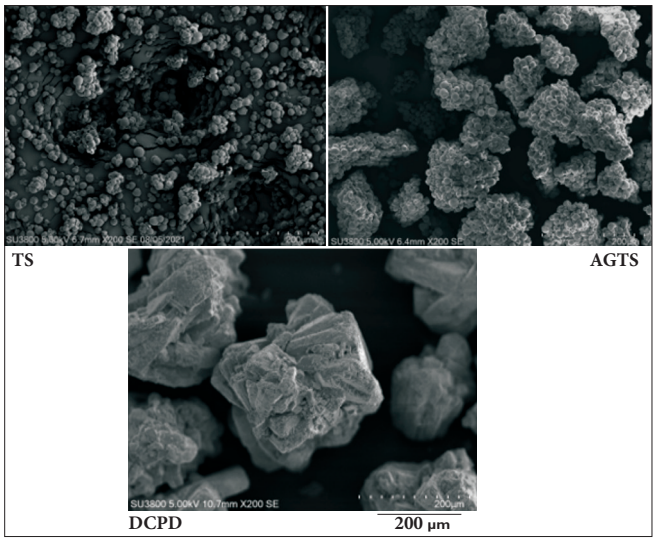

Figure 1. Particle Morphology of TS, AGTS, and DCPD Used in This Study.

Compressibility of the DCPD-starch Blends

Compressibility refers to the ability of a powdered material to decrease in volume, indicating powder deformation, when subjected to compression pressure.[36,37] To assess the compressibility and deformation characteristics of the materials, tablets were produced by applying varying compression pressures. The resulting out-die tablet thicknesses were measured, and the data were used to conduct Heckel plots (Equation 3), as shown in Figure 2a and 2b. The Heckel plot showed good fitting, with R^2 values greater than 0.92 in the range of 31.2–124.9 MPa pressures. The parameters involved in this plot are listed in Table 3. DCPD showed the lowest K value, whereas TS showed the highest, and AGTS had a slightly lower K value than TS. The K value from this analysis represented plastic deformation under pressure; the greater the K value, the greater the plastic deformation.[32] The P_y (yield pressure) value for DCPD was 432.9 MPa, and those for TS and AGTS were 122.6 and 127.9 MPa, respectively. The Da value (total degree of densification) could be ranked as follows: DCPD > AGTS > TS. Using the Kawakita analysis, the relationship between P/C and compression pressure (Figure 2c and 2d) showed good linearity, with R^2 greater than 0.99 in the fitting range 31.2–187.3 MPa. The a value, representing the total decrease in powder volume, for DCPD was higher than that for TS and AGTS, which showed similar a values. The P_k value, obtained from the reciprocal of the b value, was related to the yield strength of powders. The lowest P_k value was

Table 1. Particle Size of TS, AGTS, and DCPD.

Materials	D(4, 3) (µm)	D10 (µm)	D50 (µm)	D90 (µm)	Span
TS	42.92 ± 0.05	15.02 ± 0.22	36.25 ± 0.17	75.39 ± 0.31	1.67 ± 0.01
DCPD	276.79 ± 2.86	174.83 ± 2.47	270.59 ± 3.01	389.71 ± 3.24	0.79 ± 0.01
AGTS	134.98 ± 0.35	76.96 ± 0.27	134.41 ± 0.30	195.36 ± 0.54	0.88 ± 0.01

Note: Data are mean ± SD, n = 3.

Table 2. Densities and Flowability of DCPD-TS and DCPD-AGTS Blends at Various Ratios.

Components	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	True Density (g/cm^3)	Carr's Index (%)	Angle of Repose (°)
DCPD	0.984 ± 0.015	1.035 ± 0.016	2.379 ± 0.040	4.92 ± 0.07	32.17 ± 0.25
DCPD:TS					
0.75:0.25	0.992 ± 0.014	1.101 ± 0.017	2.138 ± 0.063	9.92 ± 0.14	32.37 ± 0.56
0.5:0.5	0.649 ± 0.006	0.723 ± 0.007	1.889 ± 0.057	10.27 ± 0.89	35.22 ± 0.18
0.25:0.75	0.498 ± 0.004	0.663 ± 0.006	1.655 ± 0.040	24.90 ± 0.18	36.06 ± 0.81
TS	0.387 ± 0.004	0.536 ± 0.004	1.512 ± 0.011	27.45 ± 0.25	39.04 ± 0.78
DCPD:AGTS					
0.75:0.25	0.702 ± 0.012	0.746 ± 0.008	2.168 ± 0.027	5.84 ± 0.92	32.74 ± 0.41
0.5:0.5	0.548 ± 0.008	0.585 ± 0.005	1.778 ± 0.013	6.39 ± 0.72	33.74 ± 0.73
0.25:0.75	0.492 ± 0.003	0.533 ± 0.007	1.585 ± 0.021	7.79 ± 0.74	33.61 ± 0.16
AGTS	0.392 ± 0.004	0.460 ± 0.005	1.422 ± 0.015	14.70 ± 0.91	32.40 ± 0.50

Note: Data are mean ± SD, $n = 3$.

observed in DCPD, whereas AGTS and TS were clearly higher, suggesting that DCPD required the lowest pressure for deformation.

DCPD showed lower plasticity (lower K value) with higher yield pressure (P_y). Moreover, it possessed low yield strength (P_k) and lower resistance to volume reduction under pressure. The surface morphology and internal structure of the DCPD tablet were observed using SEM, as shown in Figure 3. SEM revealed that most DCPD particles were fractured under pressure. This outcome suggested that the volume of DCPD powder could be reduced under low pressure by fragmentation, and fragmented particles could be rearranged and fused by plastic deformation at high pressure. The deformation of DCPD in this study was similar to that reported previously.[32,38] On the other hand, starches showed greater resistance to volume reduction (higher P_k values) and greater plasticity (higher K values and lower yield pressures) than DCPD under pressure. SEM analysis in Figure 3 showed the deformation of starch granules without fragmentation in TS and AGTS tablets. This result confirmed the presence of plastic deformation and a cold-welding mechanism under pressure, leading to a hard, compact product. However, particle size effects of TS and AGTS were observed, similar to previous reports showing that particle size affects the compressibility and deformation of materials.[30,33] AGTS showed lower yield strength and higher yield pressure than TS, suggesting that its larger size could be deagglomerated and deformed under pressure before cold-welding between particles to form a compact.

The Heckel and Kawakita plots are the most commonly used for characterizing the compaction behavior and mechanical properties of powders, particularly plasticity.[39] Both plots of the DCPD-TS and DCPD-AGTS blends are presented in Figure 2. Blending of TS or AGTS into DCPD caused an increase in K value, and a reduction of P_y value was found when using the Heckel analysis (Table 3). These results were similar to a blend of microcrystalline cellulose and DCP.[14] In the Kawakita analysis, a higher TS/AGTS ratio reduced the a value, whereas the P_k value increased (Table 3). These outcomes suggested that higher TS or AGTS ratios decreased yield pressure (P_y value) and increased yield strength (P_k value) of the blends, enhancing their plasticity and increasing their resistance to volume change under pressure. The surface morphology and internal structure of the DCPD-TS and DCPD-AGTS tablets at the ratio of 0.5:0.5 are presented in Figure 4. It can be seen that the smooth region on the tablet's surface was attributed to the DCPD particles being fractured. The starch granules and DCPD particles partially fused to form a compact, as observed with both TS and AGTS. The internal structure of the tablets showed that DCPD particles were embedded within the starch granules. EDX analysis was used to investigate the elemental composition of starch granules and DCPD particles in tablets (Figure 4). The TS and AGTS showed carbon and oxygen as the dominant elements. In contrast, the DCPD particles contained oxygen, calcium, and phosphorus. It can be observed that the DCPD particle surface contained 9.9% and 8.2% carbon in the DCPD-TS and DCPD-AGTS tablets, respectively. This result indicates that some starch granules may deposit on DCPD particles during plastic deformation under pressure, due to cold-welding.

Characteristics of Tablets Without a Drug

Figure 5 presents the thickness and hardness of the DCPD-TS and DCPD-AGTS tablets compressed using 62.4, 124.9, and 249.8 MPa. The thickness of the tablets decreased with increasing pressures (Figure 5a and 5b). The lowest thickness of the DCPD tablets was observed at all pressures. AGTS tablets were thicker than TS tablets. An increase in TS or AGTS ratios in the blends led to a rise in tablet thickness, with a more substantial effect observed with AGTS. Apart from tablet thickness, the hardness of DCPD tablets

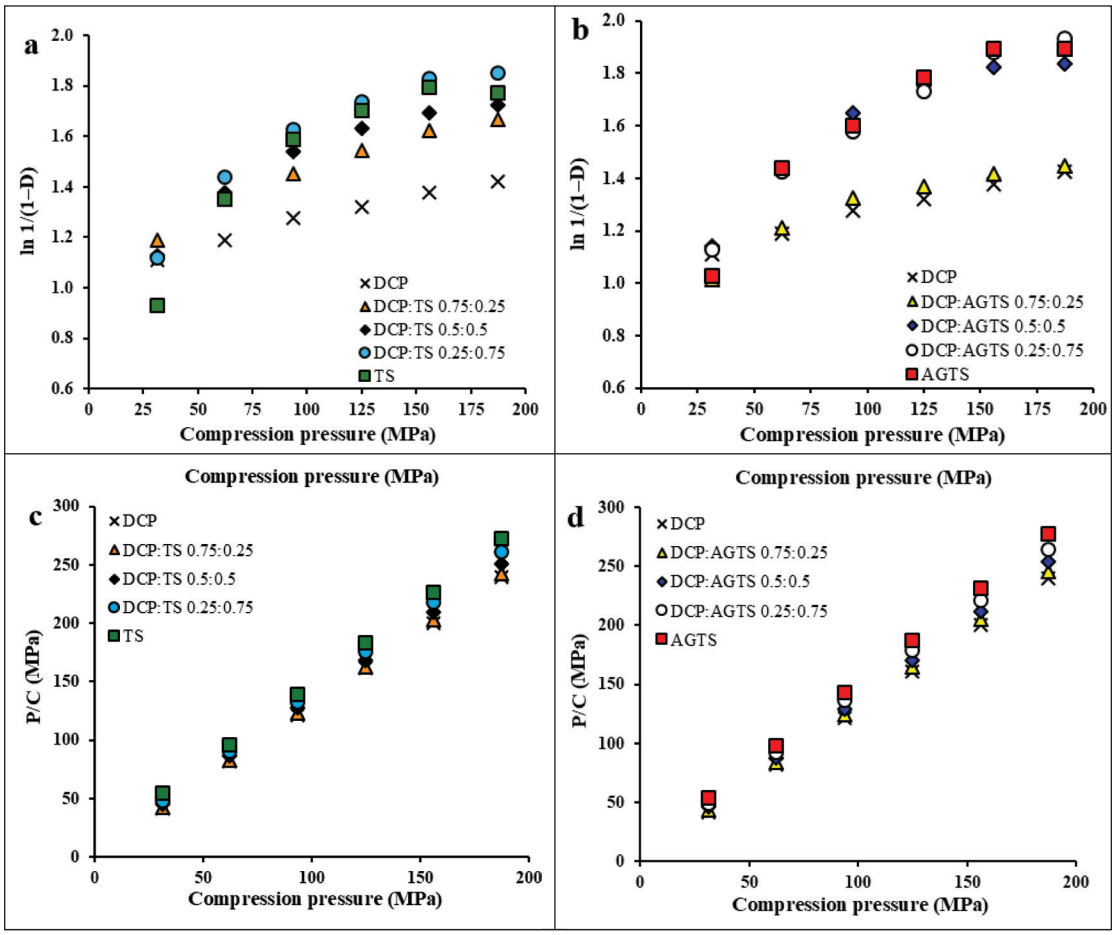

Figure 2. Heckel (a,b) and Kawakita (c,d) Plots of DCPD-TS (a,c) and DCPD-AGTS (b,d) Blends at Various Ratios. Each Point Is the Mean Value From Three Tablets.

Table 3. Heckel and Kawakita Plot Constants and Parameters of DCPD-TS and DCPD-AGTS Blends at Various Ratios.

	Heckel Plot					Kawakita Plot				
	Constants			Parameters		Constants		Parameters		
Components	$K \times 10^{-2}$ (1/MPa)	A	R^2	D_a	P_y (MPa)	Slope	Intercept	a	b	P_k (MPa)
DCPD	0.231	1.043	0.9839	0.648	432.90	1.268	2.463	0.789	0.515	1.943
DCPD:TS										
0.75:0.25	0.376	1.091	0.9783	0.664	265.96	1.278	3.047	0.782	0.420	2.384
0.5:0.5	0.534	1.003	0.9577	0.633	187.27	1.317	4.071	0.759	0.323	3.091
0.25:0.75	0.655	0.969	0.9505	0.620	152.67	1.360	5.675	0.735	0.240	4.172
TS	0.816	0.757	0.9319	0.531	122.55	1.397	9.448	0.716	0.148	6.764
DCPD:AGTS										
0.75:0.25	0.378	0.933	0.9236	0.607	264.55	1.294	3.247	0.773	0.398	2.510
0.5:0.5	0.656	0.983	0.9557	0.626	152.44	1.330	4.619	0.752	0.288	3.473
0.25:0.75	0.633	0.973	0.9672	0.622	157.98	1.372	6.987	0.729	0.196	5.092
AGTS	0.782	0.851	0.9473	0.573	127.88	1.431	8.867	0.699	0.161	6.198

obviously increased with increasing compression pressures (Figure 5c and 5d). This result suggested that a new surface area, resulting from increased fragmentation of DCPD particles at higher pressures, formed a cold-welding region, thereby increasing tablet hardness. In addition, AGTS tablets had higher hardness than TS tablets at all pressures, and

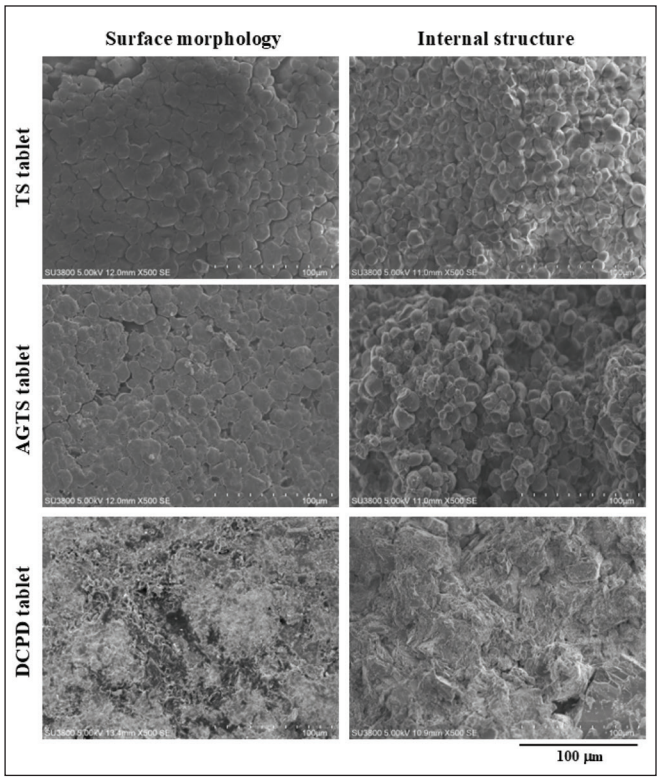

Figure 3. Surface Morphology and Internal Structure of TS, AGTS, and DCPD Tablets Prepared Using Compression Pressure of 249.8 MPa.

hardness increased with increasing pressure. However, the hardness of TS tablets at 124.9 and 249.8 MPa showed no significant difference ($p > .05$), suggesting a limitation of cold-welding and interparticle bonding of TS granules via plastic deformation at high pressure. AGTS tablets showed an increase in hardness because the surface of TS granules had a solid bridge of PVP (an agglomerating agent), which could promote cold-welding and interparticle bonding between granules.[20,26] Comparison with DCPD tablets: TS tablets had higher hardness than DCPD tablets at 62.4 and 124.9 MPa, but the opposite effect was observed at the highest pressure. In contrast, the hardnesses of the AGTS tablets were greater than those of the DCPD tablets at all pressures.

TS blending affected the hardness of DCPD tablets. The DCPD-TS tablets at 0.75:0.25 and 0.5:0.5 ratios had statistically lower hardness ($p < .05$) than the DCPD tablets at 62.4 MPa. The higher TS proportion (DCPD:TS = 0.25:0.75) resulted in a significantly greater hardness ($p < .05$) than that of DCPD tablets, at 62.4 and 124.9 MPa. However, increasing TS ratios increased tablet hardness at a compression pressure of 249.8 MPa, and the DCPD tablets also showed the highest hardness. Apart from TS, AGTS blending yielded hardness values similar to those of the DCPD tablets at 62.4 MPa. An increase in AGTS ratios led to a statistically greater hardness ($p < .05$) than the DCPD tablets at 124.9 MPa. However, the lower hardness was observed in the DCPD-AGTS tablets at ratios of 0.75:0.25 and 0.5:0.5, compared with that of the DCPD tablets at the highest pressure. However, the 0.25:0.75 DCPD-AGTS blend showed greater tablet hardness than DCPD tablets. These outcomes suggested that TS, with small particles, may hinder DCPD fragmentation, reducing the new surface area for interparticle bonding, particularly at the highest pressure and at lower hardness. The DCPD-AGTS blends showed greater tablet hardness than the DCPD-TS blends, suggesting that a larger particle size and PVP coating on AGTS particles could enhance DCPD-AGTS and AGTS-AGTS interparticle bonding during compression.

Another feature of the tablets compressed at 249.8 MPa was the disintegration time in 0.1 N HCl, as shown in Figure 6. The DCPD tablets did not completely disintegrate after 45 min. DCPD is insoluble in water but can be dissolved in an acidic environment.[40] Water penetration into DCPD tablets could occur, but no disintegration force was observed.[41] Thus, these tablets showed a slow dissolution in the medium. The TS tablets gave significantly shorter disintegration time ($p < .05$) than the AGTS tablets. It is well known that TS has been used as a disintegrant in pharmaceutical tablets.[15] Native starches were water-insoluble but were hydrophilic due to water hydration, which induced water penetration into tablet pores and reduced particle-particle bonding.[42,43] The tablets were then disintegrated. A slow rate of water penetration into pore channels was expected in the AGTS tablets because PVP films between the starch granules and the greater tablet hardness could retard this process. Thus, a longer disintegration time was found in the AGTS tablets. Blending TS or AGTS into the DCPD tablets resulted in a remarkably shorter disintegration time. This result suggested that TS and AGTS could induce water hydration and penetration into the tablets, thereby reducing particle-particle bonding of DCPD and promoting tablet disintegration. However, TS was also shown to be an effective disintegrant compared to AGTS.

Characteristics of PPN Tablets

Tablets containing 10% PPN were prepared at a compression pressure of 249.8 MPa The characteristics of the PPN tablets with various diluents are shown in Table 4. The thicknesses of the tablets were similar to those without PPN in Figure 5. The DCPD tablets with drug (63.00 ± 1.31 N) had a hardness that was indistinguishable from that without drug (63.15 ± 2.55 N). This result indicated that DCPD fragmentation, which creates new surface area for interparticle bonding, was not hindered by the presence of PPN particles, and in contrast with TS and AGTS, incorporation of PPN caused a significant reduction of tablet hardness ($p < .05$) because PPN particles, which possessed poor compressibility,[19,20] could obstruct plastic deformation for particle bonding. For more details, the TS tablets had a hardness of 42.76 ± 3.23 N (Figure 5), which decreased to 24.30 ± 1.07 N (Table 4) upon incorporation of 10% PPN at a compression pressure of 249.8 MPa.

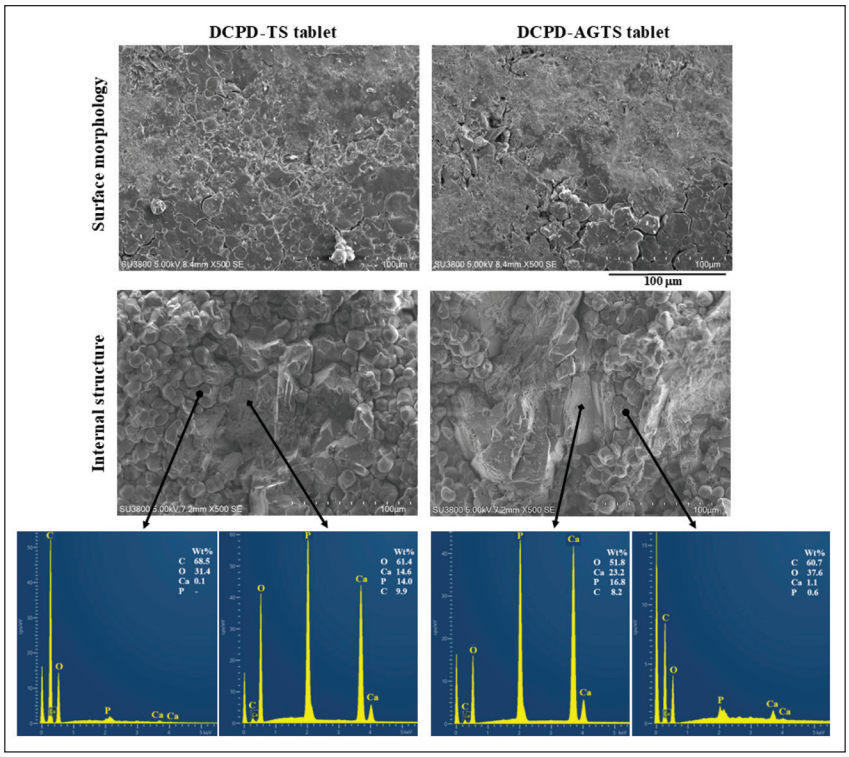

Figure 4. Surface Morphology and Internal Structure With EDX Analysis of DCPD-TS and DCPD-AGTS Tablets at 0.5:0.5 Ratio Prepared Using Compression Pressure of 249.8 MPa.

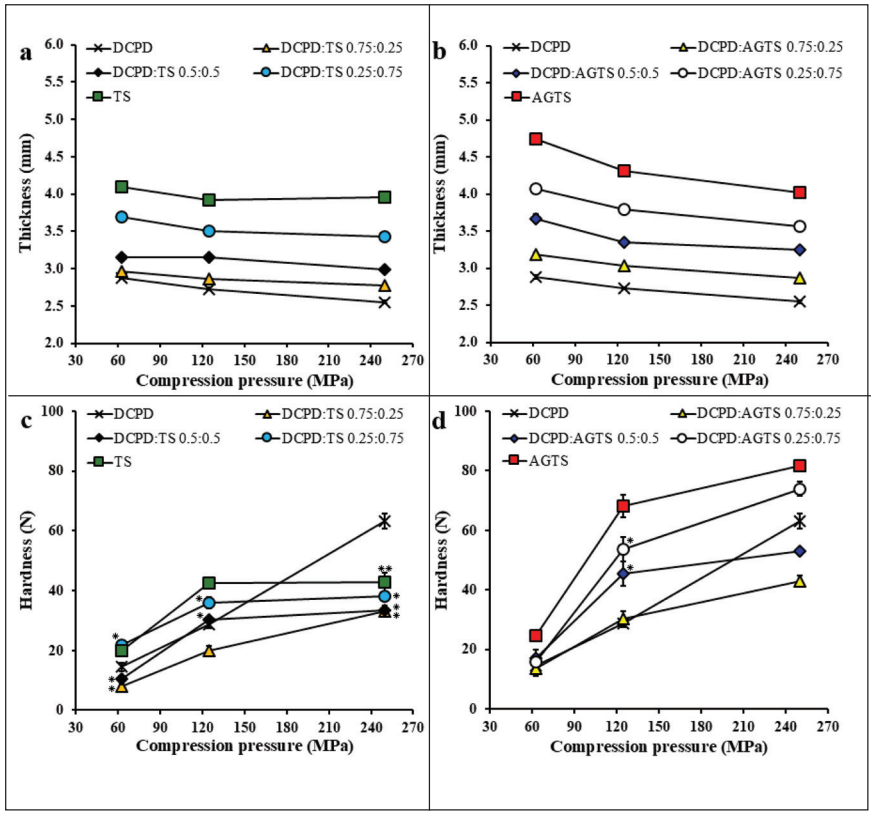

Figure 5. Thickness (a,b) and Hardness (c,d) of DCPD-TS (a,c) and DCPD-AGTS (b,d) Tablets at Different Ratios Compressed at 62.4, 124.9, and 249.8 MPa Pressures. Each Point Is the Mean ± SD From Five Tablets. *Statistically Significant Differences ($p < .05$) Compared to DCPD Tablets at the Same Compression Pressure; **Statistically Insignificant Differences ($p > .05$) Compared to TS Tablets at 124.9 MPa.

In contrast with the AGTS tablets, the hardness of 81.78 ± 0.87 N without drug decreased to 78.79 ± 0.87 N when 10% PPN was added. These outcomes suggested that the cold-welding of TS (small particles) under compression pressure was more strongly affected by PPN addition than by AGTS.

The DCPD-TS tablets with PPN tended to exhibit a decrease in tablet hardness as TS ratios increased (Table 4). On the other hand, the hardness of the DCPD-AGTS tablets statistically increased ($p < .05$) with increasing AGTS ratios. It is clarified that the larger AGTS particles still underwent effective cold-welding under compression to form a high-strength tablet, even with PPN incorporated. This was superior to TS in terms of tablet strength.

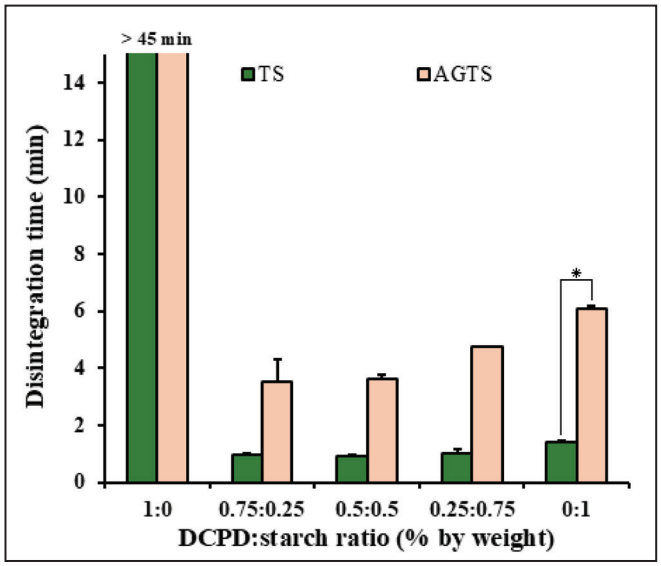

Figure 6. Disintegration Time of Tablets Prepared Using DCPD-TS and DCPD-AGTS Blends at Different Ratios. Each Point Is the Mean ± SD From Three Tablets. *Statistically Significant Differences with $p < .05$.

The disintegration time of the PPN tablets in 0.1 N HCl is listed in Table 4. The results were similar to those without PPN (Figure 6), with the longest disintegration time observed for the PPN-loaded DCPD tablets. Moreover, the PPN-loaded AGTS tablets provided a longer disintegration time than the PPN-loaded TS tablets. Increasing the TS or AGTS ratio in the DCPD-TS or DCPD-AGTS tablets resulted in a longer disintegration time. Apart from tablet disintegration, the PPN dissolution profiles of the DCPD-TS and DCPD-AGTS tablets are shown in Figure 7a and 7b, respectively, and the $T_{50\%}$ values of PPN dissolution are shown in Table 4. The DCPD tablets showed the slowest PPN dissolution, with $T_{50\%}$ exceeding 90 min because the tablets did not disintegrate; however, DCPD could slowly dissolve in a diluted acidic medium. The TS and AGTS tablets showed complete dissolution of PPN at 90 min, with similar $T_{50\%}$ values of 16.68 min for the TS tablets and 15.28 min for the AGTS tablets. For the DCPD-TS and DCPD-AGTS tablets, incorporating TS or AGTS at a 0.75:0.25 ratio resulted in faster PPN dissolution, with $T_{50\%}$ values obviously lower than those of the DCPD tablets. These outcomes suggested that tablet disintegration could be accelerated by adding TS or AGTS, thereby enhancing PPN dissolution. Increasing TS or AGTS at the 0.5:0.5 and 0.25:0.75 ratios did not result in significant differences in $T_{50\%}$ values. Still, they were significantly lower ($p < .05$) than those observed with the 0.75:0.25 ratio for the DCPD-TS or DCPD-AGTS tablets. However, the DCPD-AGTS tablets presented a statistically higher $T_{50\%}$ value ($p < .05$) than the DCPD-TS tablets at the same ratios. The higher tablet hardness of the DCPD-AGTS tablets caused this result. Additionally, this study found high variability in the $T_{50\%}$ value across some formulations. Variability in dissolution testing may be caused by factors related to the product, such as manufacturing and formulation. Another factor was not product-related, such as the dissolution testing itself.[44]

Table 4. Characteristics of PPN Tablets Prepared Using DCPD-TS and DCPD-AGTS Blends at Different Ratios.

Diluents	Thickness[a] (mm)	Hardness[a] (N)	Disintegration Time[b] (min)	$T_{50\%}$[b] (min)
DCPD	2.63 ± 0.04	63.00 ± 1.31	> 45	> 90
DCPD:TS				
0.75:0.25	2.94 ± 0.02	28.81 ± 1.11	0.83 ± 0.09	15.16 ± 7.04
0.5:0.5	3.17 ± 0.01	24.50 ± 0.87	1.18 ± 0.01	4.56 ± 1.27**
0.25:0.75	3.56 ± 0.02	22.34 ± 1.75	1.82 ± 0.25	5.14 ± 1.24**
TS	3.82 ± 0.03	24.30 ± 1.07	1.09 ± 0.01	16.68 ± 2.98
DCPD:AGTS				
0.75:0.25	2.98 ± 0.04	47.24 ± 1.28	2.01 ± 0.52	31.27 ± 6.43***
0.5:0.5	3.24 ± 0.04	54.88 ± 1.96*	3.76 ± 0.26	8.01 ± 0.49*,***
0.25:0.75	3.60 ± 0.04	63.70 ± 3.47*	4.84 ± 0.30	9.69 ± 2.69*,***
AGTS	3.96 ± 0.03	78.79 ± 0.87	6.22 ± 0.16	15.28 ± 3.59

Notes: [a]Data are mean ± SD, $n = 5$. [b]Data are mean ± SD, $n = 3$. *Statistically significant differences ($p < .05$) compared to DCPD-AGTS tablets at 0.75:0.25 ratio. **Statistically significant differences ($p < .05$) compared to DCPD-TS tablets at 0.75:0.25 ratio.***Statistically significant differences ($p < .05$) compared to DCPD-TS tablets at the same ratio.

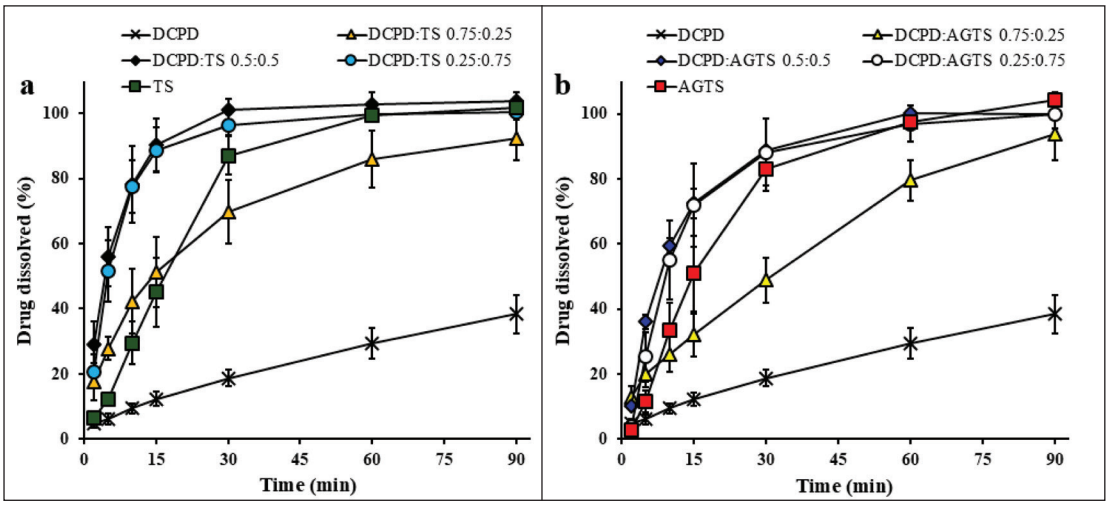

Figure 7. Drug Dissolution Profiles of PPN Tablets Prepared Using DCPD-TS and DCPD-AGTS Blends at Different Ratios. Each Point Is the Mean ± SD From Three Tablets.

Conclusion

The combination of DCPD with TS or AGTS can be used as a diluent for directly compressed tablets. DCPD demonstrates better flowability than AGTS due to its lower cohesiveness under static conditions. Conversely, the smaller particle size of TS results in higher dynamic friction than that of both DCPD and AGTS. As the proportion of TS in the blends increases, the flowability of DCPD decreases. Enhanced plastic deformation and resistance to volume change during compression are achieved by decreasing yield pressure and increasing yield strength as the TS or AGTS ratio increases. The hardness of AGTS tablets consistently exceeds that of DCPD tablets across all pressure levels. The TS tablets exhibit higher hardness than the DCPD tablets at lower pressures, whereas the DCPD tablets surpass the TS tablets in hardness at the highest pressure tested. Additionally, the DCPD-AGTS blends yield greater PPN tablet hardness than the DCPD-TS blends. The PPN-loaded DCPD tablets exhibit the longest disintegration time and the slowest PPN dissolution rate in an acidic medium. Incorporation of TS or AGTS into PPN-loaded DCPD tablets accelerates disintegration time and PPN dissolution rates. These results indicate that AGTS effectively modifies the characteristics of DCPD tablets and provides advantages over TS in terms of flowability and tablet mechanical strength, although TS provides faster tablet disintegration. Finally, DCPD-AGTS blends demonstrate sufficient flowability and compressibility to produce acceptable tablets by direct compression.

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Authors' Contribution

All authors made substantial contributions to conception and design, acquisition of data, or analysis, and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors requirements/guidelines.

Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Data Availability Statement

All the data are available with the authors and shall be provided upon request.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This study does not involve experiments on animals or human subjects.

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Informed Consent

Not applicable.

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Use of Artificial Intelligence-assisted Tools

The authors declare that they have not used artificial intelligence (AI) tools for writing and editing of the manuscript, and no images were manipulated using AI.

Supplemental Material

Supplemental material for this article is available online.

ORCID iD

Thaned Pongjanyakul https://orcid.org/0000-0001-7173-1933

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