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Functionality of wet-granulated disintegrant in comparison to directly incorporated disintegrant in a poorly water-soluble tablet matrix

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ABSTRACT

Tablet disintegration is crucial for drug release and subsequent systemic absorption. Although factors affecting the disintegrant's functionality have been extensively studied, the impact of wet granulation on the performance of disintegrants in a poorly water-soluble matrix has received much less attention. In this study, the disintegrants, crospovidone (XPVP), croscarmellose sodium (CCS) and sodium starch glycolate (SSG), were wet-granulated with dibasic calcium phosphate dihydrate as the poorly water-soluble matrix and polyvinylpyrrolidone as the binder. The effect of wet granulation was studied by evaluating tablet tensile strength and disintegratability. Comparison between tablets with granulated or ungranulated disintegrants as well those without disintegrants were also made. Different formulations showed different degrees of sensitivity to changes in tablet tensile strength and disintegratability post-wet granulation. Tablet tensile strength decreased for tablets with granulated disintegrant XPVP or CCS, but to a smaller extent for SSG. While tablets with granulated XPVP or CCS had increased disintegration time, the increment was lesser than for SSG, suggesting that wet granulation impacted a swelling disintegrant more. The findings showed that tablets with wet-granulated disintegrant had altered the disintegrant's functionality. These findings could provide better insights into changes in the disintegrant's functionality after wet granulation.

1. Introduction

The tablet is the most common solid dosage form due to its advantages: compactness, easy administration, handling and transportation, good stability, and cost-effective production (Alderborn, 2013). It typically consists of the active ingredient(s) and excipients to facilitate manufacturing and use-related performance or quality attributes. Tablet disintegration is one of the critical quality attributes of tablets, as disintegration is often the first step for drug release and bioavailability.

The most efficient tablet production process is through direct compression, where the formulation components are mixed and directly tableted. However, direct compression is only suitable for formulations with reasonable flowability (Bolhuis and Armstrong, 2006; Jivraj et al., 2000). Granulation is often necessary to minimize segregation or content non-uniformity (Alderborn, 2013; Cantor et al., 2008). Among the granulation techniques, wet granulation involves liquid addition. As contact with water is the pre-requisite for activating disintegration mechanism for disintegrants, the wet granulation process may impair the functionality of the disintegrant, resulting in delayed tablet disintegration or even failure to disintegrate.

The functionality of the disintegrant can be affected by moisture in the environment, attributed mainly to its ability to interact with water molecules (Khan and Rhodes, 1975; López-Solís and Villafuerte-Robles, 2001; Quodbach and Kleinebudde, 2014). Exposure of disintegrants to high humidity conditions could impair their performance, resulting in slower tablet disintegration (Hiew et al., 2016; Quodbach and Kleinebudde, 2015). Besides the disintegrant, the water solubility of the tablet formulation has also been demonstrated to affect tablet disintegration. Sacchetti et al. reported that the degree of increment in tablet disintegration time following storage of tablets at 75 % RH/40° C varied with the formulations' disintegrant type and aqueous solubility. The largest increment in disintegration time was observed in water-soluble and

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hygroscopic formulations, and the smallest in water-insoluble and non-hygroscopic formulations (Sacchetti et al., 2017). In a similar study, consideration of the water solubility of the formulation was shown to be important when selecting the suitable disintegrant (Bauhuber et al., 2021). More recently, the importance of temperature on disintegration has been established (Basaleh et al., 2020; Zheng et al., 2022).

Wet granulation is widely associated with tablet manufacturing, and many granulation research studies focused on the mode of disintegrant incorporation: intragranular, extragranular or a combination of intragranular and extragranular addition. However, there has yet to be a clear consensus on the ideal method of disintegrant incorporation. For starch in sulphadiazine tablets, it was concluded that extragranular starch incorporation resulted in faster tablet disintegration than intragranular addition or a combination of both methods (Shotton and Leonard, 1972). With naproxen-based tablets, it was demonstrated that extragranular croscarmellose sodium resulted in faster tablet disintegration (Gordon et al., 1990). A similar observation was also reported for co-processed mannitol and tapioca starch (Adeoye and Alebiowu, 2014). However, in metronidazole-based tablets, the intragranular addition of sodium starch glycolate or croscarmellose sodium resulted in a faster disintegration than the extragranular counterparts (Apeji et al., 2019). Another study also showed that the location of the disintegrant, sodium starch glycolate or crospovidone, had little effect on the disintegration time of lactose-based tablets, suggesting that the location of the disintegrant had little impact if the tablet matrix is water-soluble (van Kamp et al., 1983). The contradictory findings could be related to differences in the disintegrant type, tablet matrix properties and processing parameters. By wet granulating only the neat disintegrant powder, it was reported that the impaired functionality of the pre-granulated disintegrant was attributed to its larger particle size. The study suggested that decreasing the particle size of the pre-granulated disintegrant could improve the disintegrant's performance (Zhao and Augsburger, 2006a). However, the findings may not be directly transferable as the granulation was performed on the disintegrants alone in the absence of other formulation components.

Existing studies on wet granulation of disintegrants mainly focus on granulation process parameters and their impact on the resultant granules and tablets properties (Khan, 2021; Thapa et al., 2019). Crospovidone (XPVP), croscarmellose sodium (CCS) and sodium starch glycolate (SSG) are the most commonly used disintegrants in tablets. In ideal conditions, these disintegrants could produce comparable disintegration performance but studies have reported distinctly different outcomes due to storage conditions and water-solubility of the formulations (Basaleh et al., 2020; Hiew et al., 2016). Furthermore, studies performed using water-soluble matrices could be confounded by the effect of granulation on the performance of the disintegrant. Water-soluble matrices are also less sensitive to the distribution of the disintegrant in the tablet matrix (Ekmekciyan et al., 2018; Zheng et al., 2023). For tablet formulations of poorly water-soluble high-dose drugs, tablet disintegration is crucial for drug release and subsequent systemic absorption, which is pivotal in formulating immediate-release dosage forms. Therefore, a good understanding of how processing by wet granulation affects the functionality of disintegrants is needed, particularly for disintegrants with different disintegration mechanisms and in a poorly water-soluble or water-insoluble tablet matrix. This study aimed to examine the effect of wet granulation on disintegration time and tensile strength of disintegrant-containing tablet matrices comprising dibasic calcium phosphate dihydrate (DCP) with polyvinylpyrrolidone as the binder. The poorly water-soluble tablet matrix was used to reduce interference of the formulation's water solubility with the tablet disintegration process. The effect of tablet compression pressure on the disintegrant's functionality was also concurrently evaluated.

2. Materials and methods

2.1. Materials

The disintegrants investigated were crospovidone (XPVP; Kollidon CL, BASF, Germany), croscarmellose sodium (CCS; Ac-Di-Sol, FMC BioPolymer, USA) and sodium starch glycolate (SSG; Primojel, DFE Pharma, Germany). DCP (Di-Cafos D9, Budenheim, Germany) and polyvinylpyrrolidone (Kollidon 25, BASF, Germany) were used as the diluent and binder, respectively. Magnesium stearate (MgSt; M−125, Productos Metalest S.L., Spain) was used as a lubricant in tableting.

2.2. Preparation of granules

Granulation was performed using a bottom-driven high-shear granulator (PMA-1, GEA Pharma Systems, UK). The disintegrant concentration investigated was within the typical concentrations used in tablet formulations: 2 – 5 %, w/w for XPVP, 0.5 – 5 %, w/w for CCS and 2 – 8 %, w/w for SSG (Rowe et al., 2009). The polyvinylpyrrolidone concentration was selected based on the minimum concentration needed to produce intact granules. The granule final formulation comprised DCP, disintegrant and polyvinylpyrrolidone in a dry weight ratio of 90:3:7 %, w/w. Polyvinylpyrrolidone was dissolved in purified water to give a 25 %, w/w binder solution. Weighed DCP and disintegrant amounts were blended at 350 rpm impeller speed for 3 min. The binder solution was subsequently added to the powder mixture through a spray nozzle at an atomizing pressure of 1.6 bars and a 400 g/min flow rate. The impeller and chopper speeds were maintained at 500 rpm for 5 min during the wet massing. The resultant wet mass was then deaggregated using a cone mill (Comil 197S, Idex-Quadro Engineering, Canada) equipped with a 6350 μm square aperture sieve and square impeller rotating at 1239 rpm. The granules produced were dried in an oven at 60° C for 2 h. The dried granules were then subjected to milling using the same cone mill operated at 1239 rpm with a 1143 μm round aperture sieve and a round impeller. For easy reference, the disintegrant directly incorporated in the tablet matrix without undergoing wet granulation is referred to as ungranulated, while the disintegrant that has undergone wet granulation is termed as granulated disintegrant.

Granulation was also carried out to produce DCP granules without disintegrant. The granules were made of DCP and polyvinylpyrrolidone in a dry weight ratio of 93:7 %, w/w. Briefly, DCP powder was wet granulated with the 25 %, w/w polyvinylpyrrolidone solution. The subsequent granulation and milling processes were as described above. These resultant granules were used for producing tablets with ungranulated disintegrant and tablets without disintegrant (Table 1) to investigate the impact of wet granulation on disintegrant functionality.

2.3. Morphological evaluation

The morphology of the ungranulated and granulated disintegrants and DCP were examined using a scanning electron microscope (SEM; JSM-6010LV, Jeol, Japan). The sample was mounted on a sample holder using copper tape and sputter coated with platinum (MSP-2S, IXRF Systems, USA) before observation with 2 kV accelerating voltage at 250 × magnification for the ungranulated samples and 50 × magnification for the granulated samples.

2.4. Granule characterization

2.4.1. Determination of granule moisture content

Moisture content was determined using a moisture analyzer (HE73, Mettler Toledo, Switzerland). Approximately 600 mg of the granules was dried at 105° C and the sample mass before and after drying was used to calculate the moisture content using Eq. (1). Average moisture content was calculated from triplicate readings.

Table 1
Type and composition of tablets evaluated for tensile strength and disintegration time.

A) Tablets with granulated disintegrant		
Filler material*	**Disintegrant**	**Lubricant**
99 %, w/w XPVP-containing DCP granules	#	1 %, w/w MgSt
99 %, w/w CCS-containing DCP granules	#	1 %, w/w MgSt
99 %, w/w SSG-containing DCP granules	#	1 %, w/w MgSt
B) Tablets with ungranulated disintegrant		
Filler material**	**Disintegrant**	**Lubricant**
96 %, w/w DCP granules	3 %, w/w XPVP	1 %, w/w MgSt
96 %, w/w DCP granules	3 %, w/w CCS	1 %, w/w MgSt
96 %, w/w DCP granules	3 %, w/w SSG	1 %, w/w MgSt
C) Tablets without disintegrant		
Filler material**	**Disintegrant**	**Lubricant**
99 %, w/w DCP granules	-	1 %, w/w MgSt

* The granules were prepared by adding 25 %, w/w polyvinylpyrrolidone solution to a powder mixture containing DCP and the disintegrant.
** The granules were prepared by adding 25 %, w/w polyvinylpyrrolidone solution to DCP powder.
# Disintegrant added intragranularly in the filler material.
- No disintegrant in the formulation.

$$\text{Moisture content}\,(\%) = \frac{\text{initial sample mass} - \text{sample mass after drying}}{\text{initial sample mass}} \times 100 \quad (1)$$

2.4.2. Characterization of granule size

A laser diffraction sizer (LS230, Beckman Coulter, USA) with a pre-installed dry powder module was used to determine granule size and size distribution. The cumulative undersize distribution curve was generated to obtain the D_{10}, D_{50} and D_{90} values, which correspond to the 10^{th}, 50^{th} and 90^{th} percentiles of the granule size, respectively. Granule size distribution was described using the span and calculated using Eq. (2). The characterization tests were performed in triplicates, and the averaged values were reported.

$$\text{Span} = \frac{D_{90} - D_{10}}{D_{50}} \quad (2)$$

2.5. Production of tablets

Tablets (300 mg each) were made using a semi-automatic tablet press (NP-RD10A, Natoli Engineering Company, USA). The tablets were produced at 64, 127 and 191 MPa compression pressures with a 10 mm flat-face punch and die set (Natoli Engineering Company, USA).

Tablets evaluated were summarized in Table 1. Three sets of tablets were produced, a set using the disintegrant-containing DCP granules (Table 1A) and two others using the DCP granules without disintegrant (Tables 1B and 1C). For the first set of tablets, the disintegrant-containing DCP granules were blended with 1 %, w/w MgSt for 3 min and tableted. For the second set of tablets, the DCP granules without disintegrant were first mixed with 3 %, w/w disintegrant extra-granularly for 3 min, followed by mixing with 1 %, w/w MgSt for another 3 min before tableting. The last set of tablets was produced with DCP granules without disintegrant. These DCP granules were mixed with 1 %, w/w MgSt for 3 min before tableting.

2.6. Tablet characterization

2.6.1. Determination of tablet tensile strength

Five randomly chosen tablets were used to determine the breaking force using a hardness tester (TBF 1000, Copley Scientific, UK). Tablet thickness and diameter were measured using a digital micrometer gauge (No. 543-402BS, Mitutoyo, Japan). The tensile strength of each tablet was calculated based on Eq. (3) and the average results reported.

$$\text{Tensile strength} = \frac{2 \times F}{\pi \times D \times H} \quad (3)$$

where F refers to the breaking force. D and H are the tablet diameter and thickness, respectively.

2.6.2. Determination of tablet porosity

Tablet porosity was calculated from Eq. (4).

$$\text{Tablet porosity} = 1 - \frac{\rho_{app}}{\rho_{true,mix}} \quad (4)$$

where ρ_{app} is the apparent density and is calculated using Eq. (5). $\rho_{true,mix}$ is the true density of the tablet formulation and calculated according to Eq. (6).

$$\rho_{app} = \frac{W}{\pi \times r^2 \times H} \quad (5)$$

where W is the tablet weight. r and H are the tablet radius and thickness, respectively.

$$\frac{1}{\rho_{true,mix}} = \sum_{i=1}^{n} \frac{x_i}{\rho_i} \quad (6)$$

where x is the weight fraction of the component in the tablet formulation. n is the number of components in the tablet formulation. ρ is the true density of the individual components, measured using a helium pycnometer (Pentapycnometer, Quantachrome Instruments, USA).

2.6.3. Evaluation of tablet disintegration

The disintegration time of the tablets was determined using a tablet disintegration apparatus (DT2, Sotax, Switzerland) at 37° C in purified water. The test was performed with at least five randomly chosen tablets, and the results were averaged.

Disintegration time-compression pressure profiles of the tablets were constructed, and the area under the curve (AUC) was approximated using the trapezoidal rule. To assess the effect of wet granulation on the functionality of the disintegrant, the reworking efficiency was computed based on the AUC of tablets with ungranulated disintegrant and the AUC of tablets with granulated disintegrant, using Eq. (7) (Gould and Tan, 1985).

$$\text{Reworking efficiency}\,(\%) = \frac{\text{AUCungranulated disintegrant}}{\text{AUCgranulated disintegrant}} \times 100 \quad (7)$$

2.7. Statistical analysis

A general full factorial design was employed for each disintegrant to evaluate the effects of different levels of the factors investigated at the same time. The factors assessed were tablet compression pressure and tablet preparation method. Three different levels of tablet compression pressure were assessed, 64, 127 and 191 MPa. Tablet preparation methods evaluated were tablets produced from ungranulated and granulated disintegrants. For tablets prepared using the ungranulated disintegrants, DCP granules were tableted directly with the disintegrants (direct compression). The tablets containing granulated disintegrants were prepared by using disintegrant-containing DCP granules. The experimental design was generated using the statistical software Minitab (Minitab® 17.1.0, Minitab Inc., USA). The same software was used to analyze each factor's main and interaction effects on the response.

One-way analysis of variance (ANOVA) was performed using the statistical software SPSS (IBM® SPSS® Statistics, Version 20, USA) to

evaluate statistically significant differences in the reworking efficiency of the disintegrant. Bonferroni post-hoc test was performed to identify statistical differences in the disintegration time of the different tablets.

3. Results

3.1. Granule morphology

SEM showed considerable changes in the morphology and size between the granulated and ungranulated disintegrants and DCP (Fig. 1). The granules were larger than the ungranulated materials and appeared as agglomerates. In its ungranulated state, XPVP has porous sponge-like structures. Ungranulated CCS has elongated strand-like structures, while ungranulated SSG appeared as spherical particles with smooth surfaces. Ungranulated DCP appeared as irregular flakes.

3.2. Granule properties

The moisture contents of the batches of granules produced were less than 2 % (Table 2) and were not expected to confound the evaluation of the granulated disintegrant functionality. However, the size and size distribution of the granules produced with the different disintegrants showed considerable differences. The granules produced with CCS were generally smaller, with the widest size distribution as indicated by its span value (Table 2).

Table 2
Granule properties.

Granule type	Moisture content (%)	D_{10} (μm)	D_{50} (μm)	D_{90} (μm)	Span
Granulated XPVP	1.51 ± 0.10	61.55 ± 2.41	345.67 ± 12.11	764.40 ± 12.90	2.03 ± 0.04
Granulated CCS	1.14 ± 0.21	55.67 ± 1.43	143.17 ± 3.87	556.63 ± 11.72	3.50 ± 0.02
Granulated SSG	0.97 ± 0.10	34.33 ± 2.39	532.90 ± 5.80	950.03 ± 9.07	1.76 ± 0.07
Granulated DCP	1.94 ± 0.10	42.73 ± 9.25	489.20 ± 19.80	950.93 ± 17.56	1.92 ± 0.12

± represents standard deviation

3.3. Tablet tensile strength

Fig. 2(i) shows the tensile strength of the tablets. The tablets without disintegrant were generally mechanically stronger than the disintegrant-containing tablets. For tablets containing ungranulated disintegrants, tablets containing ungranulated CCS and SSG had similar tensile strength and higher than the tensile strength of tablets containing ungranulated XPVP. However, in tablets containing granulated disintegrants, tablets containing granulated SSG had higher tensile strength than corresponding tablets containing granulated XPVP and CCS at all the compression pressures investigated. The effect wet granulation of the disintegrant had on the resultant tablets' tensile strength was more apparent for tablets with granulated XPVP or CCS. These tablets had lower tensile strength than tablets with the corresponding ungranulated disintegrants. The effect of wet granulation on SSG on tablet tensile strength was not apparent. Therefore, the impact of wet granulation on the tablet tensile strength was not similar for all three disintegrants and at all the compression pressures investigated (Fig. 2(ii)). When comparing ungranulated and granulated disintegrants, a negative change in the tablet tensile strength indicates lower tablet tensile strength when the disintegrant was incorporated intragranularly. In comparison, a positive change indicates higher tablet tensile strength. Tablets containing granulated XPVP showed a greater difference in tensile strength with increasing compression pressure, while tablets containing granulated CCS had the opposite trend. In contrast, the ungranulated and granulated SSG-containing tablets remained relatively unaffected over the compression pressure range used.

3.4. Tablet disintegration time

DCP tablets made without disintegrant remained intact and did not disintegrate even after 15 min. The disintegration efficiency decreased in the order XPVP > CCS > SSG for the disintegrant-containing tablets. Tablets with ungranulated disintegrants performed better, with markedly shorter disintegration times when compared between ungranulated and granulated disintegrants (Fig. 3(i)). This suggests that in a poorly-water soluble tablet matrix, the disintegrant that was ungranulated and located extragranularly had better disintegration functionality than the disintegrant that had undergone wet granulation and located intragranularly. These results also align with the findings in studies that used naproxen and acetaminophen as the poorly-soluble drug model (Adeoye and Alebiowu, 2014; Gordon et al., 1990). Therefore, the location of the disintegrant could have a greater impact in poorly-water soluble formulations than in water-soluble formulations.

Access of the disintegrant to a liquid medium to initiate its disintegration action is closely related to the tablet microstructure, which could

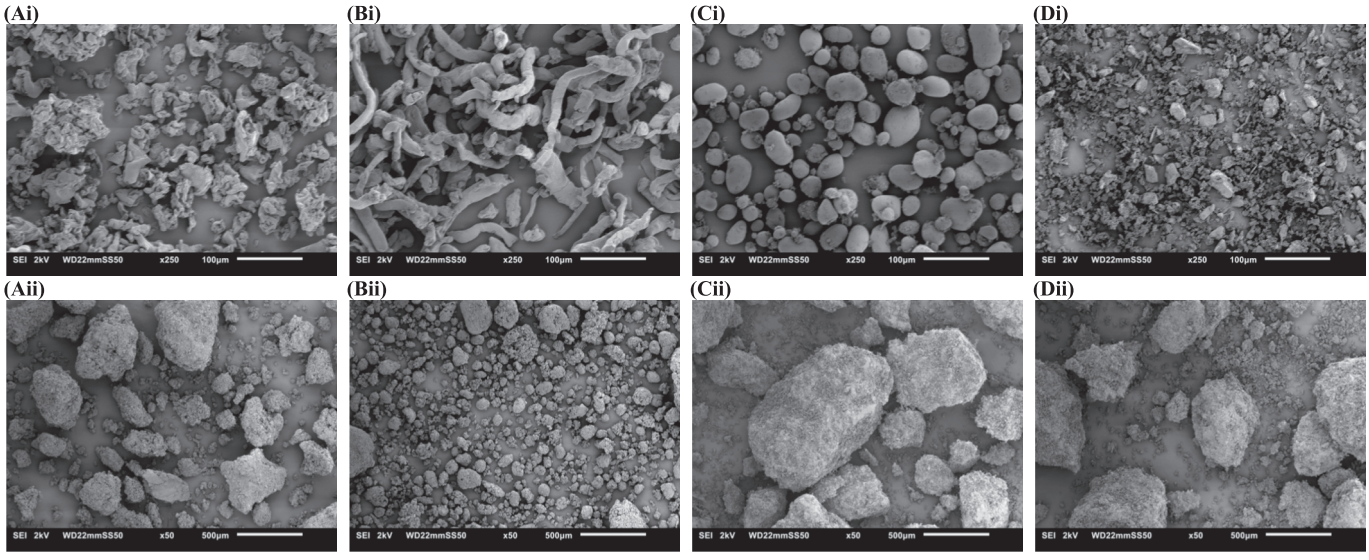

Fig. 1. Representative SEM pictures of (i) ungranulated (A) XPVP, (B) CCS, (C) SSG and (D) DCP, and (ii) granulated (A) XPVP, (B) CCS, (C) SSG and (D) DCP.

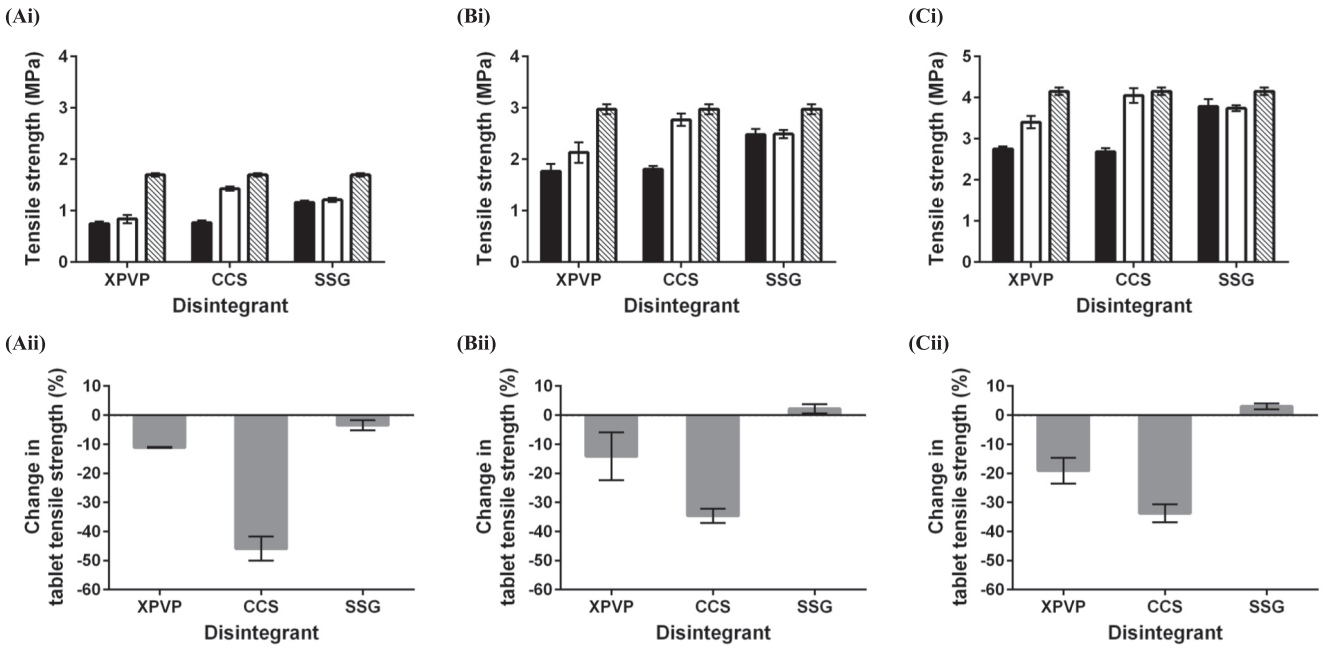

Fig. 2. Mechanical property of tablets produced at compression pressure of (A) 64 MPa, (B) 127 MPa and (C) 191 MPa. (i) Tensile strength of tablets with granulated disintegrant (■) compared to tablets with ungranulated disintegrant (□) and tablets that do not contain any disintegrant (▨). (ii) Percentage change in tablet tensile strength between tablets with granulated disintegrant and tablets with ungranulated disintegrant.

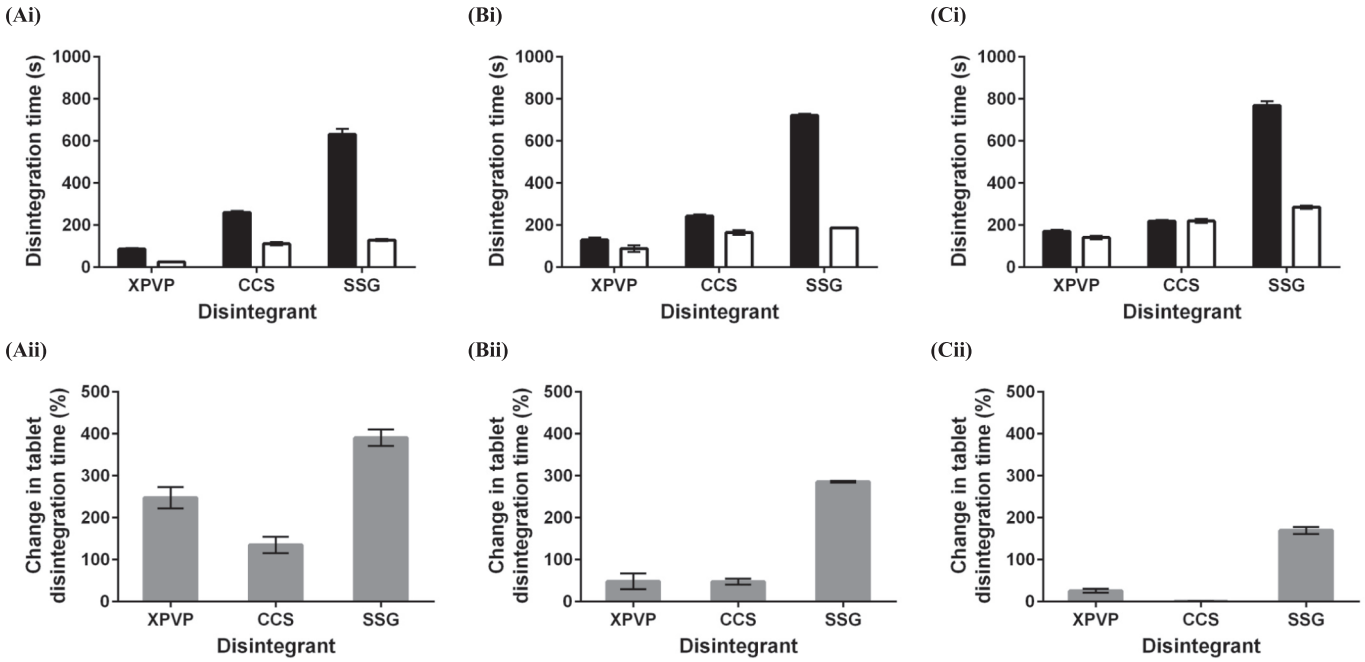

Fig. 3. Disintegration time of tablets produced at compression pressure of (A) 64 MPa, (B) 127 MPa and (C) 191 MPa. (i) Disintegration time of tablets with granulated disintegrant (■) in comparison with tablets with ungranulated disintegrant (□). (ii) Percentage change in disintegration time between tablets with granulated disintegrant and tablets with ungranulated disintegrant.

be altered by the compression pressure used in the tablet production. Hence, the disintegrant's functionality should be investigated in parallel with the changes in tablet compression pressure. The percentage change in tablet disintegration time with granulated disintegrant is presented in Fig. 3(ii). A positive change indicates a longer disintegration time than the corresponding tablets containing ungranulated disintegrant. Among the three disintegrants evaluated, CCS had the slightest change in the tablet disintegration time, while SSG, had the most. The disintegration functionality of granulated and ungranulated disintegrants in tablets could also be a function of the compression pressure. Overall, the most considerable change in the disintegration time of tablets containing granulated versus ungranulated disintegrants was observed at the lower compression pressure. With increasing compression pressure, this difference diminished, and it was more drastic for tablets containing XPVP or CCS. For tablets produced at 191 MPa, the disintegration time of tablets with granulated XPVP or CCS and their corresponding ungranulated disintegrant-containing tablets were almost comparable.

Reworking efficiency was first introduced by Gould and Tan (Gould

and Tan, 1985) to assess the efficiency of the disintegrant after reworking the disintegrant through comminution and granulation, taking into account the tablet compression pressure. It was reported that granulated disintegrant resulted in a slower disintegration. A lower reworking efficiency indicates a broader difference in the disintegration times between tablets containing granulated and ungranulated disintegrants. Therefore, the greater the deviation of the reworking efficiency from 100 %, the greater the impairment of the disintegrant's functionality following wet granulation.

Results expressed by the reworking efficiency were 72.2 % ± 9.7 %, 68.6 % ± 1.8 % and 27.7 % ± 0.4 % for XPVP, CCS and SSG, respectively. The reworking efficiency of SSG was significantly different from that of XPVP and CCS ($p < 0.001$), while the reworking efficiency of XPVP was not significantly different from that of CCS ($p > 1.000$).

3.5. Effects of compression pressure and tablet preparation method on tablet properties

The main effects plots of compression pressure and tablet preparation method, either with granulated disintegrant or ungranulated disintegrant, on the tensile strength and disintegratability of the tablets are presented in Fig. 4. The main effects plot examines differences between level means of the factors evaluated. The mean response values (disintegration time or tensile strength) for each level within the considered factors were displayed in each main effects plot. For each factor, no main effect is present when the line connecting the mean response values is horizontal (parallel to the x-axis). The absence of a main effect means that each level of the factor results in a similar response. On the contrary, deviation of the line from the horizontal position indicates an effect; hence, different levels of the factor result in different responses. A line with a steeper gradient suggests a greater effect.

Compression pressure and tablet preparation method had significant

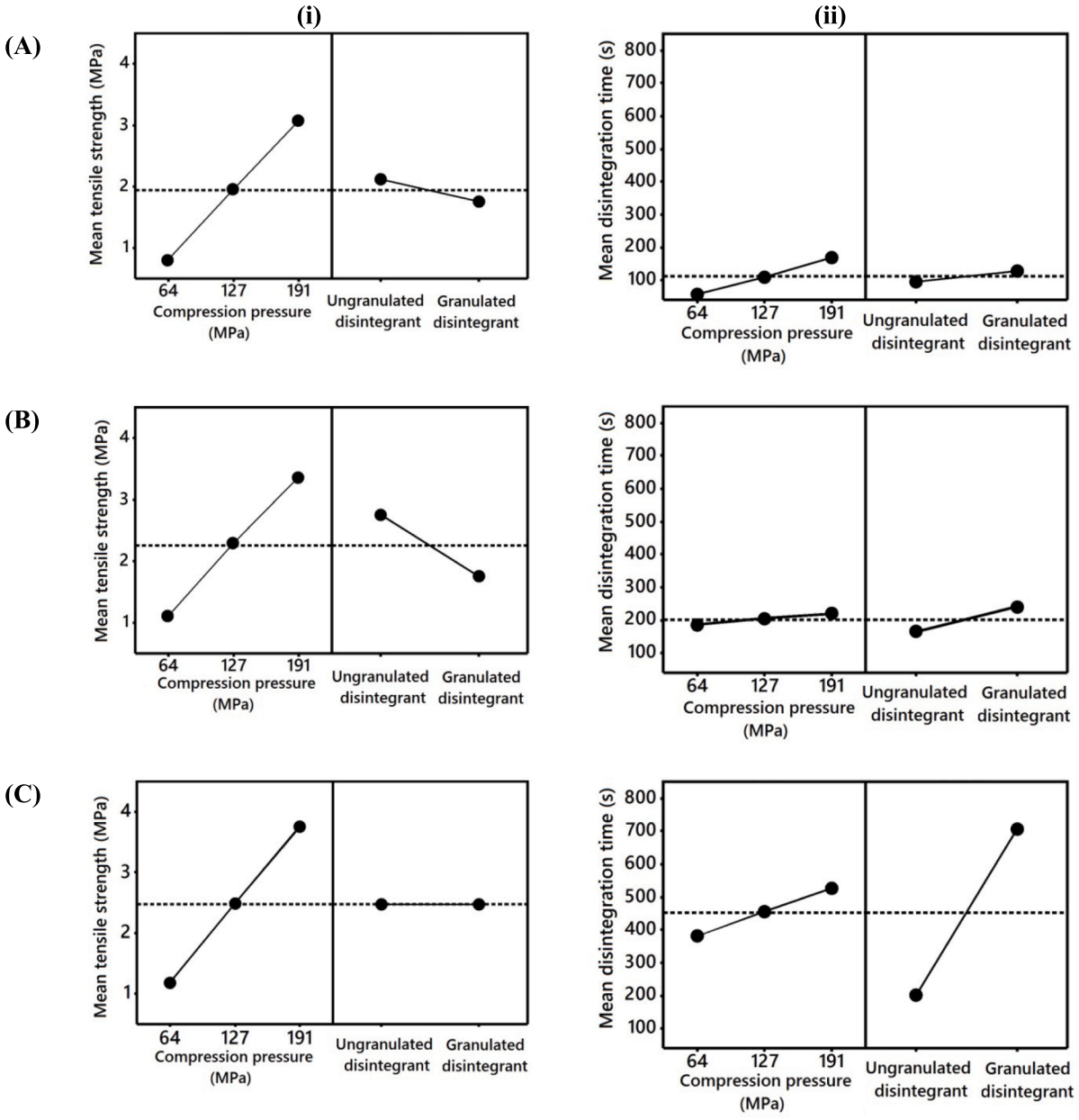

Fig. 4. Main effects plots of compression pressure and tablet preparation method (with granulated disintegrant or with ungranulated disintegrant) on (i) tablet tensile strength and (ii) tablet disintegration time. Disintegrants: (A) XPVP, (B) CCS and (C) SSG.

main effects on the tensile strength and disintegration time of tablets containing XPVP and CCS ($p < 0.001$) (Fig. 4A-4B). While compression pressure significantly affected the tensile strength of tablets containing SSG ($p < 0.001$), the tablet preparation method did not ($p = 0.836$) (Fig. 4C(ii)). Compression pressure had a greater impact on tablet tensile strength than on tablet disintegration time, as seen from the steeper line. Among the disintegrants, compression pressure affected disintegratability least for tablets containing CCS. On the contrary, the effect of the tablet preparation method on disintegratability was most prominently observed in tablets containing SSG. These findings suggested that the different disintegrants have different susceptibilities to change in their functionality following wet granulation.

3.6. Interactions between compression pressure and tablet preparation method on tablet properties

Two-way interactions between compression pressure and tablet preparation method were evaluated. The interaction plots evaluate whether one factor's effect depends on the level of the other factors. For XPVP and CCS, statistically significant interactions between compression pressure and tablet preparation method were observed for tensile strength ($p < 0.001$) and disintegration time ($p < 0.001$) (Fig. 5A-5B). However, for SSG, a significant interaction between compression pressure and tablet preparation method was present for disintegration time ($p < 0.001$) but not for tensile strength ($p > 0.001$) (Fig. 5C). These findings also corroborated the degree of change observed in tablet tensile strength (Fig. 2(ii)) and tablet disintegration time (Fig. 3(ii)) with different compression pressures.

3.7. Interrelation between tablet porosity, tablet tensile strength and tablet disintegration time

Tablet compression pressure can affect the packing of particles in the die and, in turn, tablet porosity. As matrix porosity governs the ease of water penetration, the inter-relationships of porosity, tensile strength and disintegration time of the tablets prepared were examined. Compared to tablets containing granulated XPVP or CCS, it was observed that the porosity of tablets containing granulated SSG was slightly lower (Fig. 6). Existing studies have reported that tablets of higher porosity had faster disintegration due to enhanced wicking of the tablet matrix (van den Ban and Goodwin, 2017; Zakowiecki et al., 2019). Similar observations were made in this study whereby increasing tablet porosity resulted in faster disintegration and lower tensile strength. However, the disintegratability of tablets with granulated CCS remained almost comparable regardless of the tablet porosity. Generally, a gradual rightward shift was observed for tablets with granulated

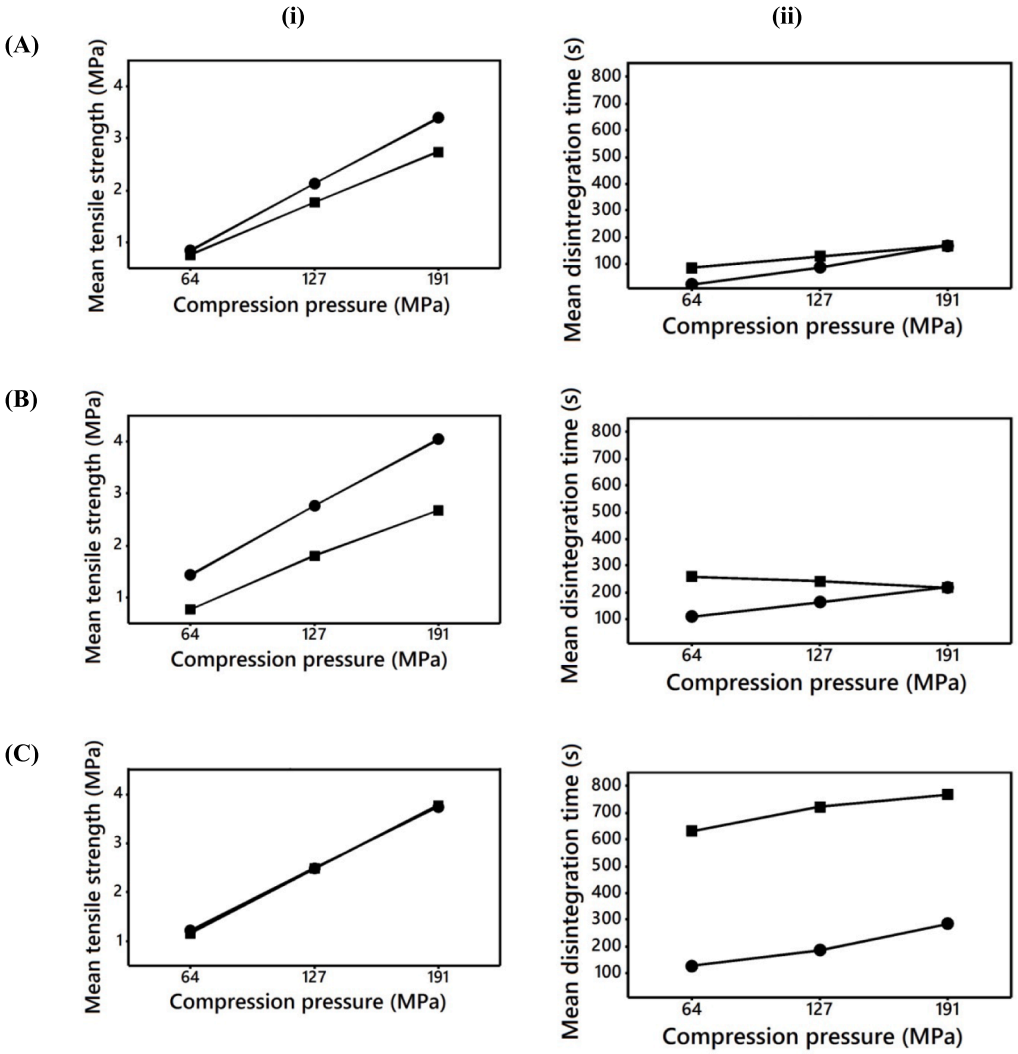

Fig. 5. Two-way interactions plots between compression pressure and tablet preparation method (with granulated disintegrant (■), with ungranulated disintegrant (●)) on (i) tablet tensile strength and (ii) tablet disintegration time. Disintegrants: (A) XPVP, (B) CCS and (C) SSG.

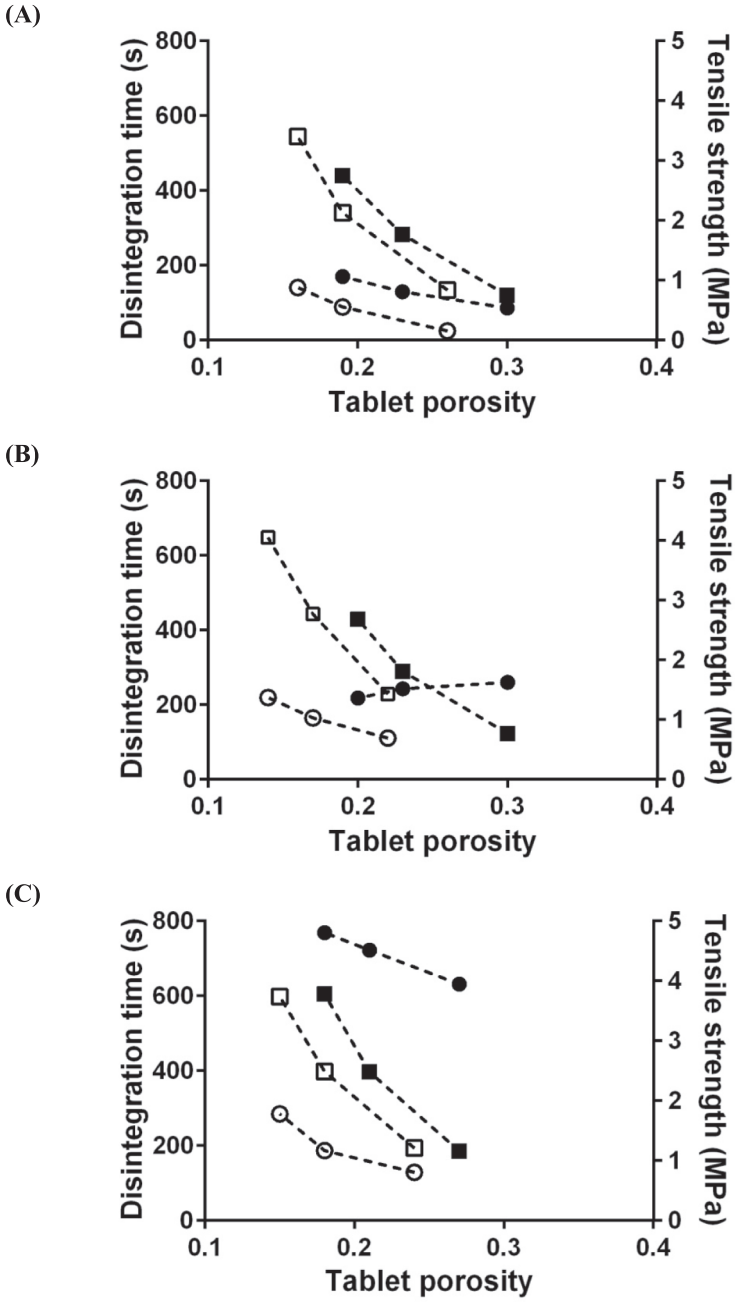

Fig. 6. Relationship between tablet porosity with disintegration time (●,○) and tensile strength (■,□) in tablets with granulated disintegrants (closed symbol) and tablets with ungranulated disintegrants (open symbol). Disintegrants: (A) XPVP, (B) CCS and (C) SSG.

disintegrant compared to tablets with ungranulated disintegrant at each compression pressure investigated, thus suggesting that the tablets containing granulated disintegrant were more porous, which could affect the time needed for the disintegrant to come into contact with water to exert its disintegration action. Due to their comparatively larger particle size, the granulated disintegrant had poorer packing, resulting in tablets of higher porosity than those containing ungranulated disintegrant.

4. Discussion

4.1. Effects of wet granulation of the disintegrant on tablet tensile strength

Tablet tensile strength arises from the interaction between the matrix components by the process of building bond area and strong bonds (Sun, 2012). Thus, tablet tensile strength can be affected by the constituents in the formulations and by how they are processed before tableting, such as the granulation method. The reduced tablet tensile strength observed when a disintegrant was added into the tablet formulations could be due to the impairment of the cohesive bonding between the DCP granules.

While the processing of materials before tableting could affect tablet tensile strength, the effect differed with the material type. This is evident as the granule size and size distribution differed for the formulations with different disintegrants (Table 2). Since the same concentration of binder solution was used for all the formulations, differences in the properties of the granules could be attributed to the disintegrants used. Several studies have observed differences in the binding properties of XPVP, CCS and SSG (Kornblum and Stoopak, 1973; Sheen and Kim,

1989; Zhao et al., 2017). Wet granulation resulted in the densification of the powder mass, and denser granules could be produced. The denser granules are more resistant to fragmentation. Hence, the granules have poor compressibility. As a result, tablets containing granulated disintegrants had the lowest tensile strength. Similar findings have been reported in a hydrophobic formulation produced using a high-shear wet granulation. The study identified that the ratio of liquid to solid components in the formulation was critical for particle agglomeration to produce dense granules, which could result in tablets with reduced tensile strength (Liu et al., 2022). Variations in the granule size distribution for tablets containing granulated disintegrants or DCP granules also affected the tablet tensile strength.

The lower tensile strength of the tablets with ungranulated disintegrants was notable, compared to tablets without any disintegrant. The disintegrant particles were disruptive to the good cohesive matrix of DCP, resulting in mechanically weaker tablets, albeit generally marginal when disintegrants were added. Between the granulated and ungranulated disintegrants, wet granulation could have helped to distribute the disintegrant particles better, and their effect of disrupting the binding of the DCP matrix was more effective. Nevertheless, this effect was less apparent for SSG as the more spherical shape and smaller particle size of SSG particles, granulated or ungranulated, made them less effective at disrupting matrix strength compared to CCS and XPVP.

4.2. Effects of wet granulation on the functionality of XPVP

Granulation appeared to reduce the disintegratability performance of the disintegrants, particularly for SSG. Overall, the disintegratability of XPVP and CCS was minimally affected.

As a water insoluble, synthetic cross-linked polymer (Bühler, 2005), the disintegration action of XPVP can be attributed to its ability to draw water by capillary (wicking) action and swelling (Kornblum and Stoopak, 1973). Strain recovery (shape recovery) has also been reported as the disintegration mechanism of XPVP (Desai et al., 2012; Quodbach and Kleinebudde, 2014). Several studies have reported the detrimental effects of subjecting XPVP-containing tablets to elevated RH. Reduced disintegration functionality of XPVP in tablets exposed to elevated RH has been attributed to the plasticization of XPVP by moisture, resulting in an earlier release of strain energy stored in the compacted XPVP and hence, premature disintegration action as evidenced by cracks in the tablet matrix (Quodbach and Kleinebudde, 2015).

In this study, the liquid added during the wet granulation was removed in the subsequent drying step. Furthermore, during the wet granulation, XPVP did not experience the same degree of compaction as with tableting. Thus, the reduced disintegration functionality of XPVP following wet granulation could not be ascribed to the premature release of strain energy stored in compacted XPVP. The sponge-like structure of XPVP facilitates water penetration, resulting in volume expansion. The swollen XPVP structure will shrink upon drying and expand again upon subsequent wetting (Barabas and Adeyeye, 1996). This property of XPVP has also been reported in tiaramide hydrochloride tablets containing XPVP that were subjected to wetting and drying cycles. It was observed that while the hardness of the tablets reduced after the wetting and drying cycles, there was only a slight decrease in the tablet disintegration time. The authors attributed this to the reversible swelling property of XPVP (Sheen and Kim, 1989). XPVP also had a longer T_2 relaxation time than SSG and CCS, suggesting XPVP had a weaker interaction with water molecules. This results in easier water removal and less sensitivity of XPVP to loss of disintegratability due to wet granulation (Onuki et al., 2018).

The slight increment in the disintegration time of tablets with granulated XPVP could also be due to the increase in tablet porosity (Fig. 6A). This was supported by the greater change in disintegration time for tablets produced at the lowest compression pressure (Fig. 3(ii)). The tablet's porosity can affect the disintegrant's performance. Low porosity limits liquid penetration and can cause a delay in the water contact of the disintegrant, which is needed for its activation. Therefore, the water penetration rate affects how fast the swelling disintegrant reacts to build up the force required to break the tablet matrix (Colombo et al., 1984). A very porous tablet matrix has more void spaces and consequently requires the disintegrant to expand more to reach the pore walls. Some energy could have dissipated during this expansion instead of being exerted on the tablet matrix. On the contrary, in a tablet matrix of lower porosity, there is lesser energy loss before the disintegrant reaches the pore wall as the disintegrant only needs to expand slightly to transfer the swelling energy to break the tablet matrix (Quodbach and Kleinebudde, 2016). Strain recovery also contributes to the disintegration mechanism of XPVP. The reduced differences in the disintegration time between tablets containing ungranulated and granulated XPVP produced at higher compression pressures (127 and 191 MPa) could be attributed to the strain recovery, thus suggesting that the strain recovery was minimally affected by wet granulation.

4.3. Effects of wet granulation on the functionality of CCS

The ability of CCS to disintegrate tablets has been attributed to swelling and strain recovery (Berardi et al., 2018; Zhao and Augsburger, 2006b). Tablets with granulated CCS had longer disintegration time than tablets with ungranulated CCS. Nevertheless, the difference was smaller compared to tablets containing SSG.

It was reported that the disintegration time of tiaramide hydrochloride-based tablets containing CCS decreased only slightly after the tablets were subjected to wetting and drying cycles (Sheen and Kim, 1989). It was also reported that the disintegration functionality of various disintegrants, after pre-wetting of the disintegrant, remained largely unchanged, and there was also no significant difference in the water uptake rate. In contrast, a significant reduction in the water uptake rate was observed for tablets containing pre-wetted XPVP and SSG (Zhao and Augsburger, 2006a).

The functionality of CCS was not affected greatly by wet granulation as the disintegration time of tablets with granulated CCS hardly altered with compression pressure or tablet porosity. This observation contrasted with the disintegration time of tablets with ungranulated CCS, which showed a shorter disintegration time with an increase in tablet porosity (Fig. 6B). The slight increment in the disintegration time of tablets containing granulated CCS could be due to the higher porosity of tablets with granulated CCS. This was also evident from the greater change in the disintegration time for tablets produced at lower compression pressure (Fig. 3(ii)). Although tablet porosity is essential for water penetration into the tablet matrix, a tablet matrix that is too porous can diminish the force generated by the disintegrant to break the tablet matrix. The diminishing differences in the disintegration time between tablets containing granulated and ungranulated CCS for tablets produced at higher compression pressures could be due to the strain recovery of CCS. Therefore, as with XPVP, the strain recovery of CCS was minimally affected by wet granulation.

4.4. Effects of wet granulation on the functionality of SSG

The functionality of SSG was the most affected by wet granulation as seen from the markedly prolonged disintegration time of tablets with granulated SSG (Fig. 3). The disintegration mechanism of SSG can be attributed to its ability to absorb large quantities of water, resulting in the swelling of SSG. The force generated by the swelling of SSG upon contact with an aqueous medium promote break-up of the tablet matrix into smaller fragments (Desai et al., 2016).

Although CCS could also cause tablet disintegration via swelling, its performance was less affected by wet granulation than SSG. This could be due to the disintegrants having different swelling behavior. A study that evaluated the swelling of pharmaceutical excipients in water revealed that SSG had relatively low initial swelling despite having high absorption and swelling capacity. In contrast, CCS had faster initial

swelling with a smaller absorption and lower swelling capacity (Soundaranathan et al., 2020). The high spacing between cross-linking of phosphate groups in SSG facilitates water penetration and swelling (Rojas et al., 2012), while the lack of spacing between the polymer chain in CCS limits swelling of CCS (Zarmpi et al., 2017).

During wet granulation, the high shear force could break the phosphate ester bonds that link starch chains in the SSG, resulting in the reduced functionality of SSG (Rudnic et al., 1983; Wren et al., 2017). A study has shown a correlation between the degree of phosphorus cross-linking and the rate of water uptake and disintegration of SSG-containing tablets (Abraham et al., 2016). Thus, with disruption of the phosphate ester bonds, the rate of water uptake and, hence, the initiation of swelling by SSG would be delayed, leading to longer tablet disintegration time. The broken phosphate ester bonds also caused an increase in the viscosity of the SSG suspension (Wren et al., 2017). Furthermore, it was reported that larger granules resulted when SSG with more broken phosphate ester bonds was used, as the damaged SSG behaved more like a binder. These findings explained the relatively larger SSG-containing DCP granules obtained post-wet granulation (Table 2).

Sheen and Kim suggested that the prolonged disintegration time of SSG-containing tablets after subjecting the tablets to wetting and drying cycles could be due to the irreversible swelling of SSG following moisture exposure (Sheen and Kim, 1989). This was further supported by another study that reported reduced swelling of SSG after exposure to an elevated humidity environment (75 % relative humidity) (Marshall et al., 1991). During the wet granulation, liquid addition resulted in swelling of SSG. However, the swelling was not completely reversible by removal of the added liquid. Thus, the granulated SSG remained in its swollen state even after the removal of the liquid in the subsequent drying process. When tablets containing the granulated SSG encountered water during the disintegration test, the swelling force generated by the granulated SSG was weaker as the SSG was already in a swollen state. Thus, the swelling was limited, and the swelling force might not be strong enough to disintegrate the tablets rapidly.

In addition to the compromised swelling force and water absorption of granulated SSG, the prolonged disintegration time of tablets with granulated SSG compared to the tablets containing ungranulated SSG may also be due to the tablets having higher porosity (Fig. 6). Tablet porosity governs liquid penetration into the tablets. While liquid penetration may not be directly related to the disintegration force needed to disrupt the compacted tablet's microstructure held mainly by particle–particle bonds, liquid penetration is a prerequisite preluding the initiation of the disintegration mechanisms of various disintegrants (Pabari and Ramtoola, 2012). Among the tablets containing granulated disintegrants, it was observed that tablets containing granulated SSG had a lower porosity and higher tensile strength than tablets containing granulated XPVP and granulated CCS; hence, water entry into the tablet would be restricted. As a result, the time needed for SSG to come into contact with water would be longer. A greater force was also required to break the tablet matrix. Therefore, in addition to the higher tensile strength of tablets containing granulated SSG, the slower water penetration resulted in markedly slower tablet disintegration than tablets containing granulated XPVP and granulated CCS. This also suggests that a good balance of tablet porosity, tensile strength, and disintegrant functionality is important for rapid tablet disintegration.

5. Conclusion

This study investigated the potential effect of wet granulation on the functionality of disintegrants having different disintegration mechanisms in a poorly water-soluble tablet matrix. Tablet properties. including tensile strength and porosity, were also investigated. It was observed that the extent of the change in tensile strength or disintegration time varied with tablet compression pressure. Overall, wet granulation on the disintegrants reduced tablet mechanical integrity and prolonged tablet disintegration. The effect of wet granulation, however, was not equivalent across the different disintegrants. The tensile strength of tablets containing XPVP and CCS was sensitive to wet granulation of the disintegrants. In contrast, the tensile strength of tablets containing SSG was less sensitive. In terms of functionality, a swelling disintegrant was likelier to show reduced disintegrant functionality after being subjected to wet granulation. In comparison, a disintegrant that acts partially by swelling, like XPVP and CCS, was less affected. It was also demonstrated that tablet porosity has a role in influencing the efficiency of disintegrants. The disintegration mechanism and water interaction properties of the disintegrant are crucial in determining the susceptibility of the disintegrant to the detrimental effects of wet granulation. The study findings could be useful for addressing problems related to changes in tensile strength and/or disintegration time for tablets prepared via a wet granulation method to incorporate the disintegrant.

CRediT authorship contribution statement

Natalia Veronica: Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Erinn Si Min Lee:** Visualization, Investigation. **Paul Wan Sia Heng:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Celine Valeria Liew:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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