The Investigation of Synergistic Behaviour of Excipients in Direct Compression Using a Rotary Press Simulator

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Poster Reprint AAPS 2012

Purpose

Benefits of using partially pregelatinized starch (PPS, Starch 1500®) as a multi-functional excipient in tablet formulations has been well documented.[1] A number of publications exist showing that the material is extremely versatile, being effective in a variety of processing methods for solid oral dosage forms, such as direct compression, wet granulation, dry granulation/roller compaction and encapsulation.[1-3] Starch 1500 is particularly effective with moisture sensitive actives[4-5] and in low drug dose applications.[2]

When used on its own, PPS does not provide compacts with high mechanical strength. However, when combined with other excipients in a formulation for direct compression, it produces tablets with acceptable mechanical strength and disintegration time, and exhibits synergy, enhancing the functionality of other excipients.

In this study, the benefit of combining two commonly used excipients, Starch 1500 and microcrystalline cellulose, for direct compression applications was investigated using a rotary press simulator.

Methods

The following samples were tested: partially pregelatinized starch (Starch 1500, Colorcon), microcrystalline cellulose (MCC; Microcel 102, Blanver), placebo and caffeine blends with and without colloidal silicon dioxide (CSD; CABOSIL, Cabot).

Compression Studies

Tablets (150 ± 10 mg) were produced from each sample using a Stylcam 100R simulator fitted with 7 mm flat-faced tooling and a generic 'direct cam' rotary press profile. Batches of 5 tablets were manufactured by manually filling the die.

Compaction forces of 5 kN (130 MPa), 10 kN (260 MPa) or 15 kN (390 MPa) and speeds of 5, 15 or 30 rpm, equivalent to rotary press production rates of approximately 20000, 60000 or 120000 tablets per hour (dwell times of 62, 22 or 10 msec) respectively, were used.

Heckel analysis was performed on the samples compressed at 10 kN (260 MPa) and mean yield pressures were determined at low (P_{y1}) and high (P_{y2}) speeds to enable calculation of strain rate sensitivity (*%SRS*) using Equation 1.

Equation 1.

$$\%SRS = ((P_{y2} - P_{y1}) / P_{y2}) \times 100$$

Elastic and plastic energy values were calculated from the force-displacement profiles using the Analis® software package.

Tablet Testing

For each tablet, weight, thickness (T), diameter (D) (digital micrometer, Mitutoyo), crushing strength (P, Pharmatron 6D, Dr. Schleuniger) and disintegration times were measured. Tensile strength (δt) was calculated using Equation 2.

Equation 2.

$$\delta t = 2P/\pi DT$$

Results

The results (Table 1) from the Heckel analysis show a greater compressibility of MCC compared to PPS. Although PPS can be considered as a plastically deforming material ($P_{Y2} > P_{Y1}$) it is less sensitive to compression speed in comparison to MCC as indicated by the lower *%SRS* value.

The data for the placebo and model active blends indicate that the compression behavior of the formulation closely resembles that of MCC with marginally higher mean yield pressures and similar %SRS values of around 20%. This suggests that the MCC dominates the compression mechanism of the blend.

Colloidal silicon dioxide did not have a significant affect on formulation compressibility.

Table 1. Mean Yield Pressure and Strain Rate Sensitivity Values

Sample	Py_1	Py_2	%SRS
PPS	129.5	146.6	11.7
MCC	83.0	106.9	22.3
Placebo blend without CSD	85.8	108.9	21.2
Placebo blend with CSD	90.1	110.1	18.2
Caffeine blend with CSD	86.6	112.4	23.0
Caffeine blend without CSD	94.5	117.5	19.6

Figure 1 shows the greater compressibility of MCC compared to PPS. The strength of MCC tablets increased with compression force and decreased slightly with compression speed. Although PPS tablet strength increased marginally at higher compression forces, tablets remained relatively weak.

Combinations of PPS and MCC, with and without CSD, produced compacts with acceptable tensile strength. Tablet strength was slightly reduced at higher compression speed and tablets with CSD showed a marginally higher strength, particularly when compressed at 15 kN (390 MPa).

Figure 1. Tensile Strength of Tablets Produced from Excipients and Excipient Blends Using Different Pressure and Speed (n = 5)

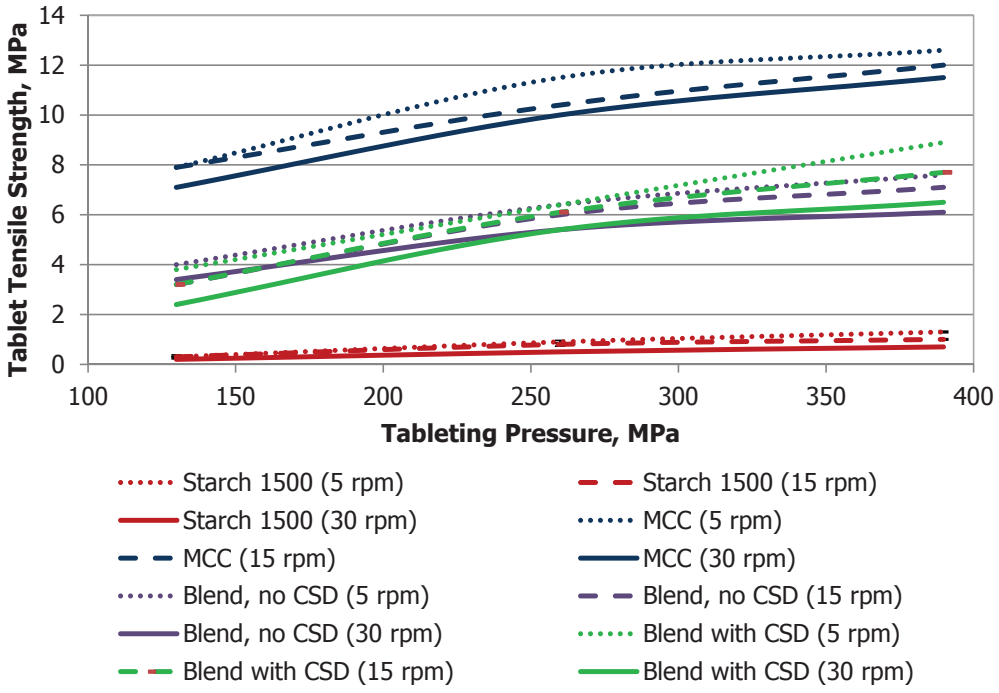
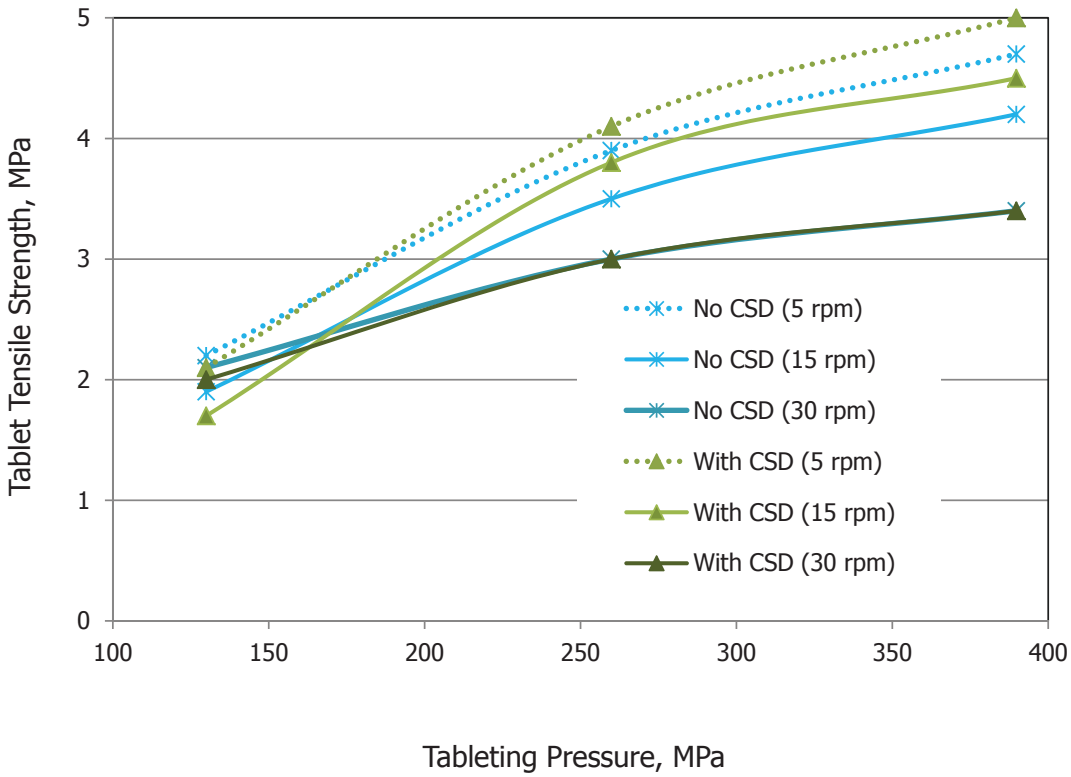


Figure 2 indicates that the presence of caffeine in the powder mixture reduced compact strength, although robust tablets were obtained when compression forces of 10 kN (260 MPa) or 15 kN (390 MPa) were employed. Similarly to previous trends, compact strength was reduced at the higher compression speed and tablets with CSD were marginally stronger, particularly when produced at 15 kN (390 MPa).

Figure 2. Tensile Strength of Tablets Produced from Caffeine Blends Using Different Pressure and Speed (n = 5)



The data calculated for compression energies (Table 2) revealed that Starch 1500 exhibited the greatest % elastic energy.

The presence of caffeine in the powder mixture increased the % elastic energy at all compression speeds and forces.

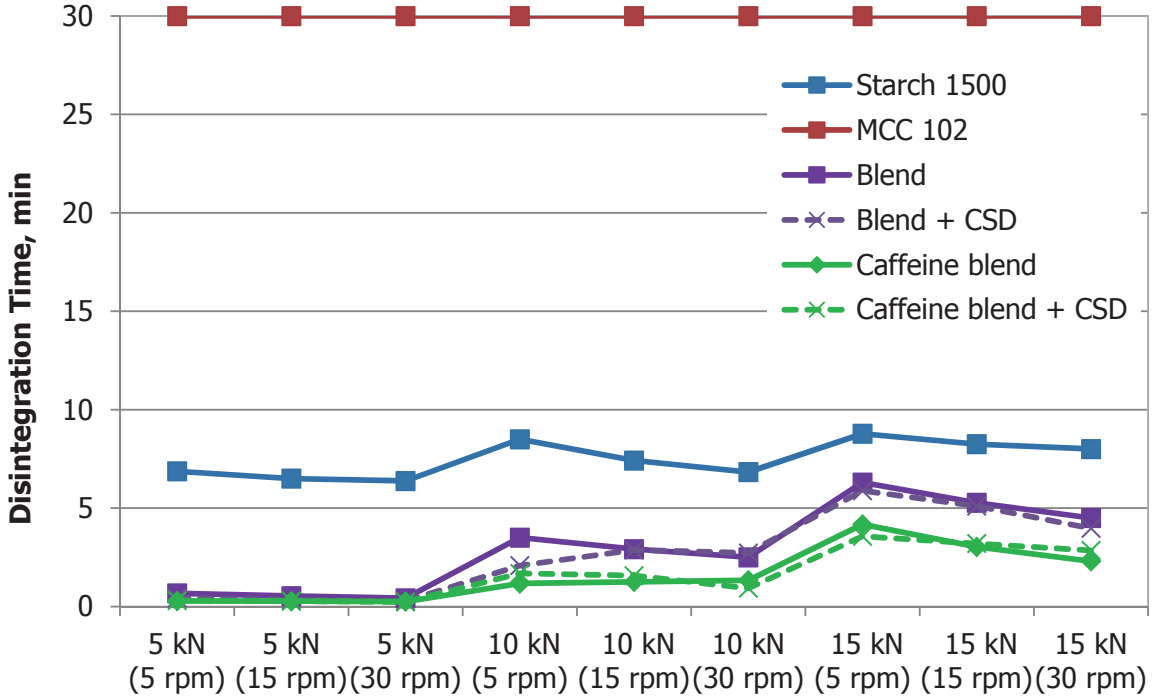
CSD did not reduce the % elastic energy for either placebo or caffeine blends.

Table 2. Percentage Elastic Energy Values

Sample	5 kN (130 MPa)			10 kN (260 MPa)			15 kN (390 MPa)		
	5 rpm	15 rpm	30 rpm	5 rpm	15 rpm	30 rpm	5 rpm	15 rpm	30 rpm
PPS	18.3	17.5	29.3	18.7	16.4	19.4	16.3	21.8	25.2
MCC	1.8	6.9	26.2	5.4	12	19.3	12.4	15.5	16.1
Blend without CSD	3.8	5.0	17.3	6.1	11.2	15.2	11.6	15.9	15.8
Blend with CSD	6.4	8.5	20.8	10.1	17.8	14.8	10.0	16.9	15.2
Caffeine blend without CSD	14.4	12.2	31.1	15.5	22.5	19.1	18.9	24.3	23.6
Caffeine blend with CSD	19.1	14.7	20.9	17.2	24.0	15.0	16.2	22.7	23.4

Figure 3 shows disintegration times of the compacts produced at different compression forces and speeds. MCC only compacts failed to disintegrate even after 30 min testing. PPS only tablets disintegrated within 6-9 min. For MCC and PPS mixtures, disintegration times were between 1 and 7 minutes, demonstrating a synergistic effect for these excipients. CSD had no significant effect on disintegration time.

Figure 3. Disintegration Time



Conclusions

- The study demonstrated a beneficial use of pregelatinized starch in a combination with MCC in direct compression. Blends of these excipients resulted in tablets with good mechanical characteristics and acceptable disintegration times.
- Combination of Starch 1500 and MCC represents a feasible option for formulation use with most drugs.
- Addition of colloidal silicon dioxide to the mixture of Starch 1500 and MCC can slightly increase tablet mechanical strength.

References

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