

Dibasic Calcium Phosphate Replacement with Starch 1500[®] in a Direct Compression Formula

Technical Data

Introduction

Dicalcium phosphate (DCP) is a commonly used filler in tablet formulas. Coarser grades of this excipient are known to flow well and have good compactibility. However, DCP is insoluble and can be very abrasive, which could cause reduced tooling life due to wear on the equipment during tablet manufacture. High levels of lubricants are required to overcome the abrasiveness, but elevated levels of hydrophobic lubricants can impact the mechanical strength of the tablets and disintegration/dissolution performance. These concerns have led to investigations of the use of other materials in tablet development.

Objective

The objective of this study was to determine whether Starch 1500[®] would be a suitable excipient choice as a replacement for dicalcium phosphate dihydrate in a direct compression formula. Starch 1500[®] is a multi-functional excipient designed specifically for use in the formulation of pharmaceutical oral solid dosage forms that is known to improve tablet properties, including disintegration

and lubricity. It is a pharmaceutical grade of partially pregelatinized maize starch manufactured exclusively for the global pharmaceutical market.

Materials and Methods

Four formulas were evaluated in this study (see Table 1). The mixtures were initially evaluated without lubricant in order to characterize the abrasiveness of each one (Formulas 1 and 2). All materials, with the exception of magnesium stearate, were blended for 10 minutes in a twin shell “V” blender. Magnesium stearate, when used, was added and blended for an additional 2 minutes. Tablets were compressed on an instrumented (SMI) Piccola (Riva) 10-station rotary tablet press using 9 mm standard concave tooling at 20 and 50 RPM.

Initial evaluations included tablet ejection force, weight, hardness, thickness, friability, and disintegration. The physical properties of the tablets were tested and documented after placing tablets in open dishes in a humidity cabinet at 40°C/ 75% RH for 2 weeks.

Table 1 - Formulas

Ingredients [Manufacturer]	Formulas without Lubricants				Formulas with Lubricants			
	Formula 1		Formula 2		Formula 3		Formula 4	
	%	mg/tablet	%	mg/tablet	%	mg/tablet	%	mg/tablet
Dibasic Calcium Phosphate Dihydrate NF [Emcompress [®] , JRS Pharma]	50.00	175.00	-	-	49.75	174.13	-	-
Pregelatinized Starch NF [Starch 1500 [®] , Colorcon]	-	-	50.00	175.00	-	-	49.75	174.13
Microcrystalline Cellulose NF [Avicel [®] PH102, FMC]	50.00	175.00	50.00	175.00	50.00	175.00	50.00	175.00
Magnesium Stearate NF [Peter Greven]	-	-	-	-	0.25	0.87	0.25	0.87
Total	100.00	350.00	100.00	350.00	100.00	350.00	100.00	350.00

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Results and Discussion

Tablet Ejection Force

Figure 1 shows the ejection forces for tableting runs performed at 20 RPM press speed. Ejection forces at the 50 RPM speed were similar. Formula 4, containing Starch 1500® and lubricant, had significantly lower ejection forces compared to Formula 3, containing DCP and lubricant. It is also important to notice the high ejection forces recorded for Formula 1, the DCP/MCC mixture containing no lubricant. After two tableting trials with Formula 1, the tooling condition deteriorated significantly.

Figure 1 – Tablet Ejection Forces at 20 RPM

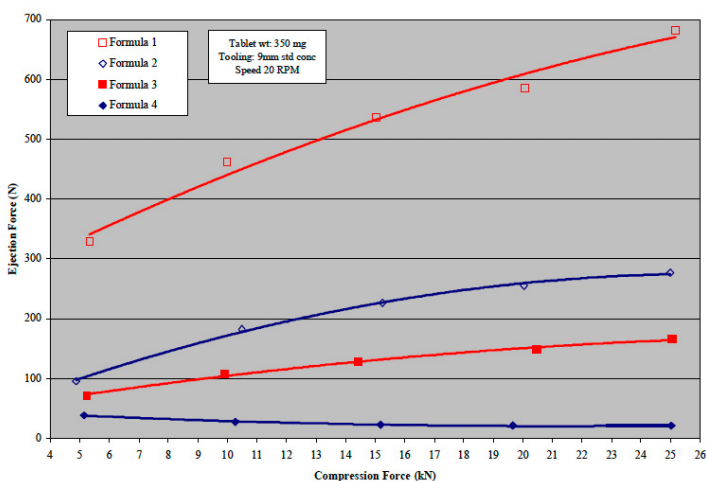
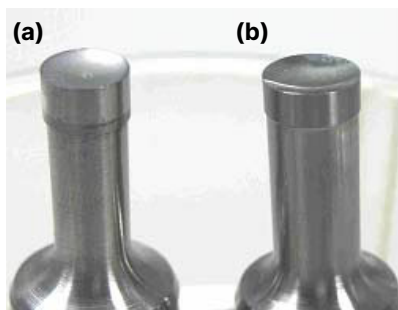


Figure 2 shows tarnished surface of the punch tip that occurred due to micro-abrasions produced by DCP particles. This demonstrates that when using brittle fracturing materials, life expectancy of tooling can be significantly shorter compared to a formula with self-lubricating materials such as Starch 1500®.

Figure 2 – Punch Tips Condition after Tableting



(a) Micro-abrasions from use of DCP particles causing worn tip.
(b) No abrasion evident when DCP is eliminated from formula

Tablet Weight + Hardness Testing

All formulas used in the study produced tablet weight variations of less than 1% at both 20 and 50 RPM. DCP mixtures produced tablets with higher mechanical strength compared to Starch 1500® (Figures 3 and 4). For a 9 mm, 350-mg tablet, it is not necessary to produce tablets with hardness in excess of 20 kp in order to withstand the stresses of further unit processes such as film coating, printing, and packaging. In comparing non-lubricated Formulas 1 and 2, to lubricated formulas 3 and 4, only a slight decrease in hardness was seen as a result of the addition of magnesium stearate. Figure 4 shows the effect of tablet speed on tablet hardnesses of both lubricated formulas 3 and 4. Only a slight decrease in hardness was seen for each formula. Plastically deforming materials can show some time-dependence on compression in contrast to DCP, which is brittle fracturing.

Figure 3 – Tablet Hardness at 20 RPM - Initial

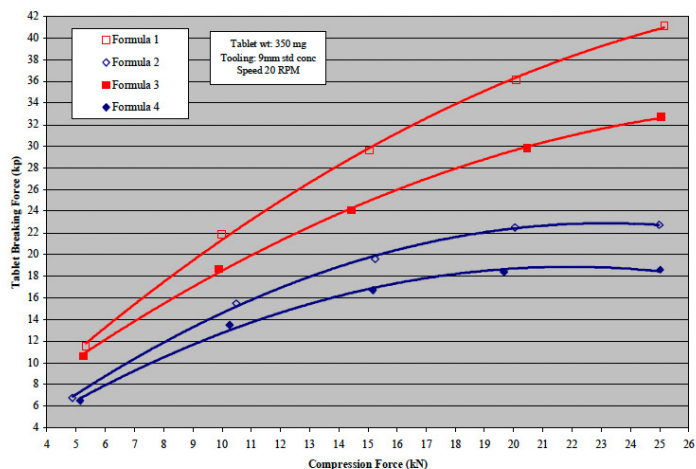
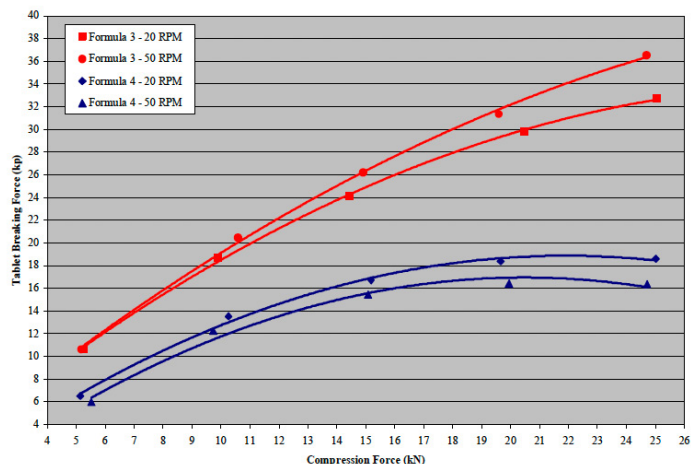


Figure 4 – Effect of Press Speed on Tablet Hardness



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Tablet Friability + Disintegration Testing

Friability values for all tablets manufactured were very low, as shown in Figure 5.

Figure 5 – Tablet Friability - Initial

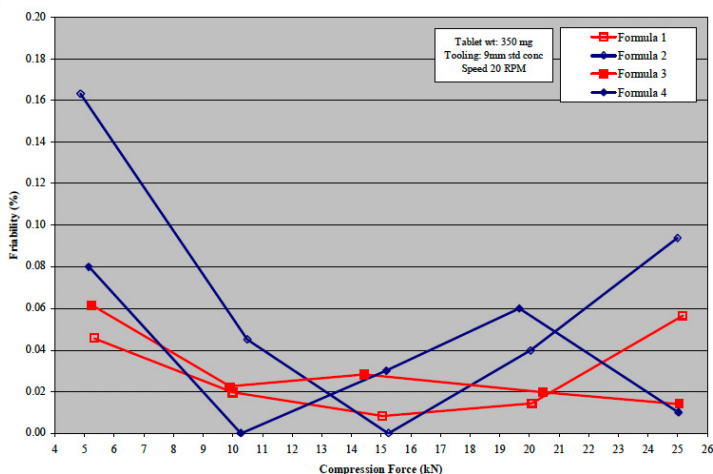
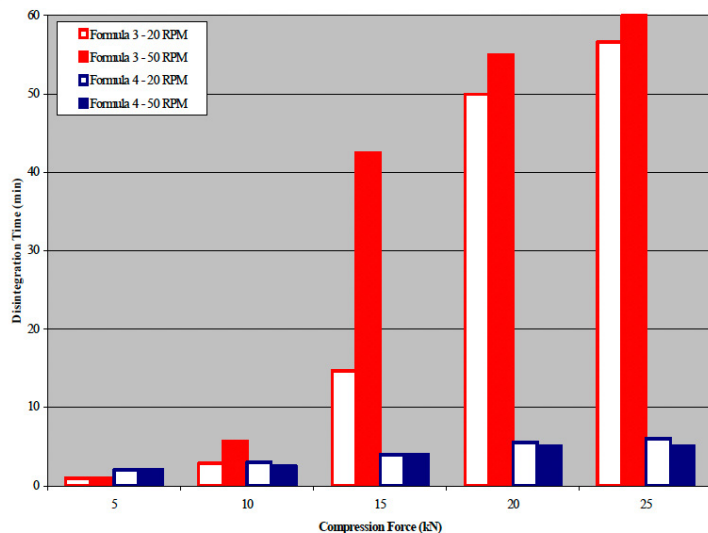


Figure 6 shows that disintegration times for tablets manufactured at the upper range of compression forces were significantly lower for Starch 1500® formulas (4–6 minutes) compared to DCP (more than 30 minutes). Some DCP tablets exceeded 60 minutes in the DT bath. These individual tablets were assigned a value of 60 minutes but actually exceeded this value. These results indicate that in direct compression, Starch 1500® has the dual functionality of a diluent and a disintegrant.

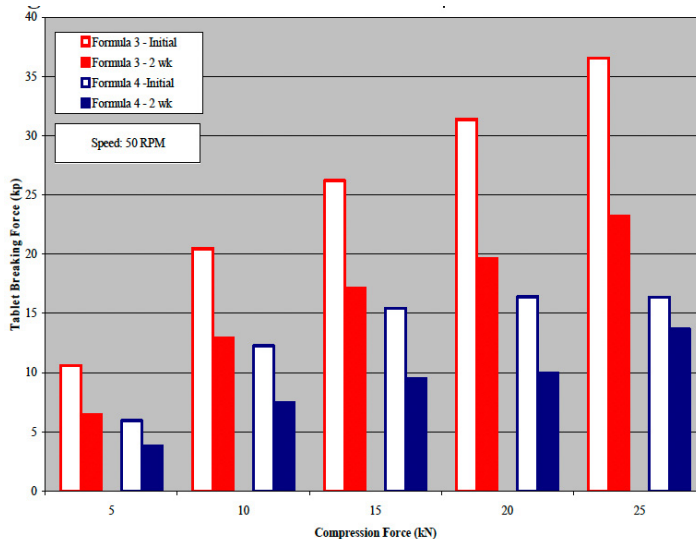
Figure 6 – Tablet Disintegration Times - Initial



Testing at Accelerated Conditions

Special attention should be given to the physical stability of the tablets manufactured by direct compression because some filler/ binders are known to soften or harden on storage. DCP dihydrate may lose its water of crystallization at elevated temperatures, resulting in tablet softening. This could have consequences on accelerated stability testing, although the material is stable under ambient conditions. In this study, conducted in open dishes at 40°C/ 75% RH, DCP tablets showed changes in mechanical strength and disintegration. Figure 7 shows the effects of storage on the lubricated formulas produced at 50 RPM. Starch 1500® showed less change in hardness over time compared to DCP.

Figure 7 – Tablet Hardness – 2 Weeks

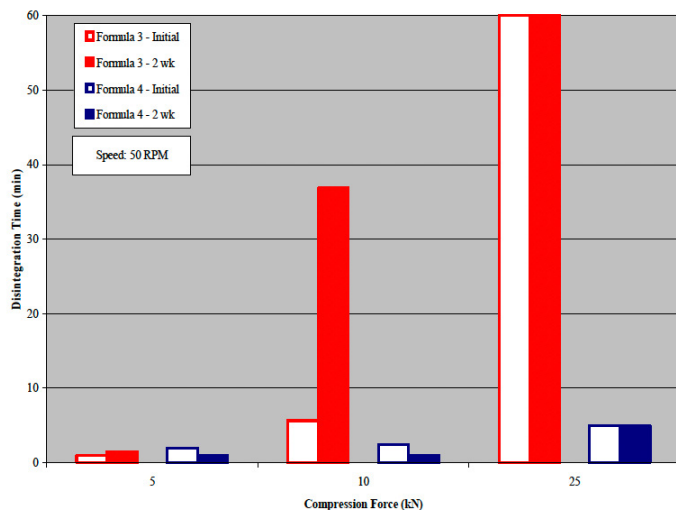


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Figure 8 shows that on storage, the DCP formulas increased in disintegration time while the Starch 1500® formulas remained constant.

Figure 8 – Tablet Disintegration Time – 2 Weeks



Conclusions

This study demonstrates that replacing DCP with Starch 1500® as an excipient would bring many benefits to a tablet formula designed for direct compression. It was found that self-lubricating Starch 1500® produced significantly lower ejection forces compared to DCP. It is important to maintain low ejection forces because high forces lead to premature machine and tooling wear. The tablet hardnesses were more than adequate in the formulas containing Starch 1500®. Press speed had little effect on these formulas.

The disintegration times of the Starch 1500®-based formulas were dramatically lower than the DCP formulas at the higher compression forces. Disintegration times for tablets manufactured at 15–25 kN was found to be significantly higher for DCP (more than 30 minutes) as compared to pregelatinized starch formulas (4–6 minutes). This study also investigated tablet behavior on storage at accelerated conditions. Despite the fact that Starch 1500® formulas produced tablets with lower mechanical strength as compared to DCP in the initial testing, these formulas were more stable under high temperature and humidity conditions.

The results clearly show that tablets containing pregelatinized starch would produce more consistent results over time and environmental changes. The use of Starch 1500® instead of DCP in a formula would not only help to reduce stress on tooling, but would also benefit formulas through improved disintegrant properties and enhanced lubricity.

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