



Lactose Replacement with Starch 1500® in a Direct Compression Formula

INTRODUCTION

Lactose is one of the most commonly used fillers in solid dosage formulas and is well known for producing tablets with high mechanical strength. Its usage has been eroded by some relatively recent concerns, such as Bovine Spongiform Encephalopathy (BSE), Variant Creutzfeldt-Jacob disease (vCJD), and lactose intolerance. These concerns have led some formulators to evaluate other excipients in their formulas. In addition, the abrasiveness of lactose can cause a decrease in tooling life due to excess wear on tableting or capsule-filling equipment. To overcome abrasiveness, lubricants must be used, but high lubricant levels can cause a decrease in tablet mechanical strength and can affect disintegration and dissolution.

OBJECTIVE

The objective of this study was to determine whether Starch 1500® would be a suitable excipient choice as a replacement for lactose in a direct compression formula.

Starch 1500® is a multi-functional excipient designed specifically for use in the formula of pharmaceutical oral solid dosage forms. Starch 1500® brings benefits to formulas through binding capability, improved disintegrant properties, and enhanced flow and lubricity. Manufactured exclusively for the global pharmaceutical market, Starch 1500® is a pharmaceutical grade of partially pregelatinized maize starch.

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. All materials, with the exception of magnesium stearate, were blended for 10 minutes in a twin shell “V” blender. Magnesium stearate 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 concave tooling at 20 and 50 RPM. Tablet hardness, ejection force, weight, thickness, friability, and disintegration times were measured.

Tablets were placed in open dishes in a humidity cabinet at 50°C/ 75% RH and tested after 1 month of storage.

RESULTS AND DISCUSSION

Testing the formulas without lubricant allows for a direct comparison of the material properties. Unfortunately, Formula 1 could not be run due to excessively high ejection forces at the lowest compression force. This indicates that any lactose formula will require the addition of a lubricant. It was possible to tablet Formula 2 containing only microcrystalline cellulose (MCC) and Starch 1500®.

Figure 1 shows the ejection forces for the tableting runs performed for each formula at 20 RPM press speed. With the same lubrication level, Formula 3

Table 1. Formulas

Ingredients [Manufacturer]	Formula 1		Formula 2		Formula 3		Formula 4	
	%	mg/tab	%	mg/tab	%	mg/tab	%	mg/tab
Lactose Monohydrate NF [Fast Flo®, Foremost]	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



produced ejection forces that were three times higher than Formula 4, which contained Starch 1500[®]. Ejection forces at the 50 RPM speed were similar to those produced at 20 RPM. Formula 3, containing lactose, produced tablets with higher tablet hardness as compared to Formula 4, containing Starch 1500[®] (see Figure 2). 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 lubricated formulas to unlubricated, only a slight decrease in hardness was seen as a result of the addition of magnesium stearate. Figure 2a shows the effect of tablet speed on hardnesses of the lubricated formulas. Only a slight decrease in hardness was seen for each formula.

Figure 1. Ejection Forces at 20 RPM

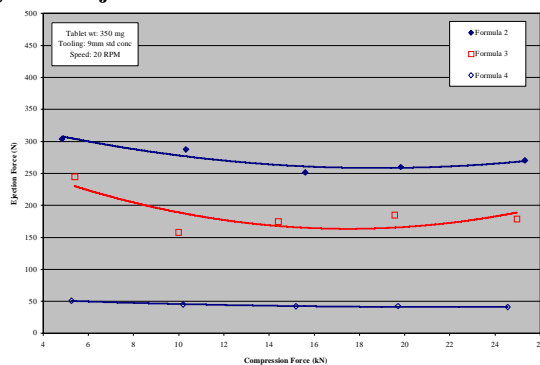


Figure 2. Tablet Hardness at 20 RPM – Initial

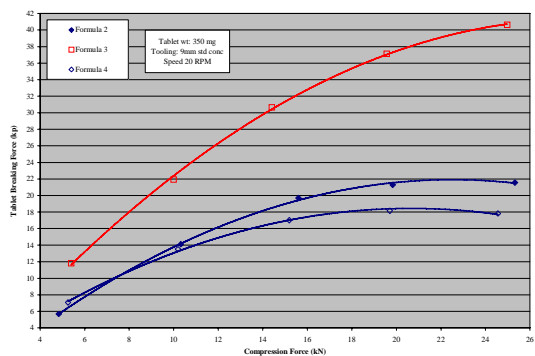
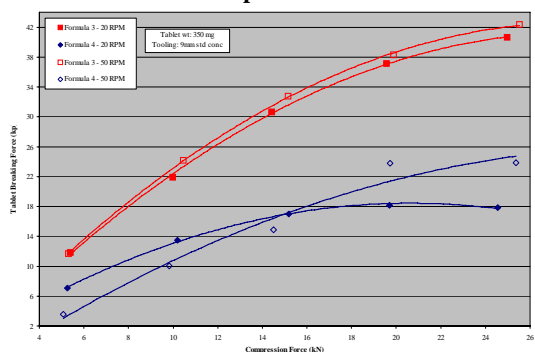


Figure 2a. Effect of Press Speed on Tablet Hardness



Starch 1500[®] and MCC are plastically deforming materials. Plastically deforming materials can show some time dependence on compression in contrast to lactose, which is brittle fracturing. All formulas used in this study produced tablet weight variations of less than 1% at both 20 and 50 RPM. Figure 4 shows tablet friability values. All tablets manufactured at 10 kN and above had zero friability. Disintegration times, shown in Figure 5, were significantly shorter for Starch 1500[®] tablets as compared to lactose tablets manufactured above 20 kN of compression force. This illustrates that in direct compression, Starch 1500[®] has the dual functionality of a diluent and a disintegrant.

Figure 3. Tablet Friability – Initial

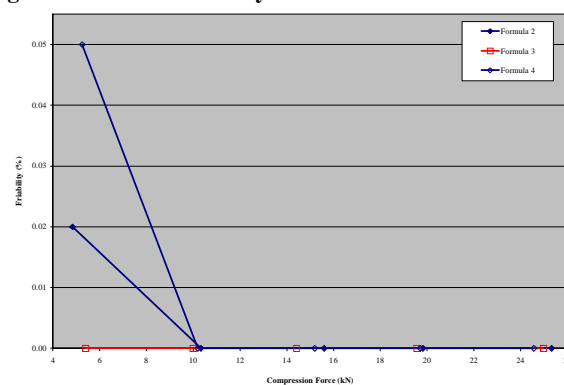
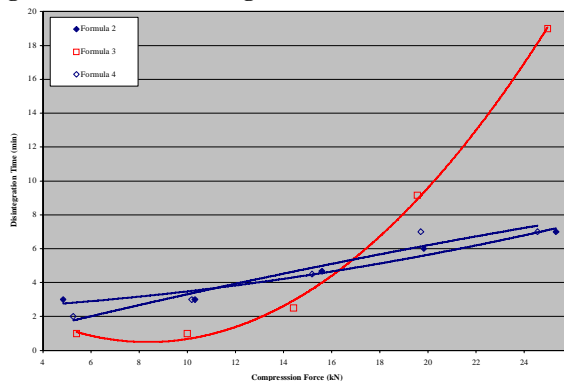


Figure 4. Tablet Disintegration Times – Initial



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. It is well known that Fast Flo[®] lactose is highly compressible, has a good flowability, and exhibits no browning reactions. The physical stability, however, is limited, particularly when the product is stored under humid conditions where softening of some products can occur. Spray-dried lactose (SDL), which contains amorphous lactose, is slightly hygroscopic. Tablets compressed from SDL tend to increase in mechanical strength during storage under normal conditions.

In this study, conducted in open dishes at 50°C/75% RH, lactose tablets, Formula 3, showed a significant deterioration in hardness (see Figure 5), and friability (see Figure 6). These parameters for Starch 1500® remained almost unchanged. Lactose tablets also showed a significant increase in tablet disintegration time (see Figure 7).

Figure 5. Tablet Hardness – 1 Month

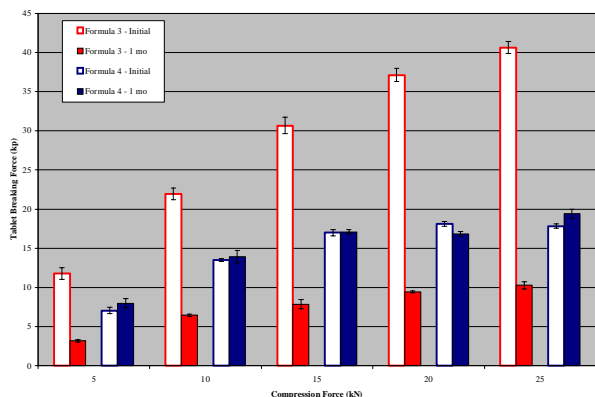


Figure 6. Tablet Friability – 1 Month

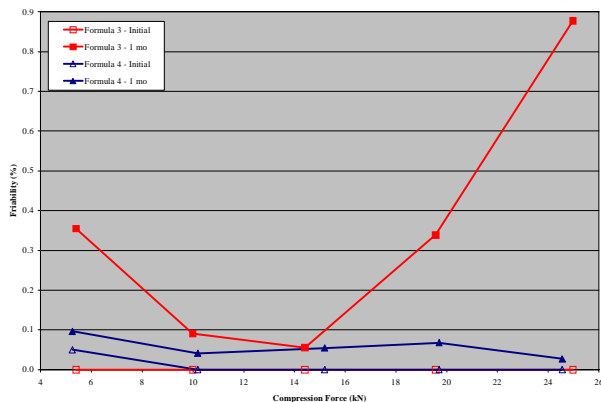
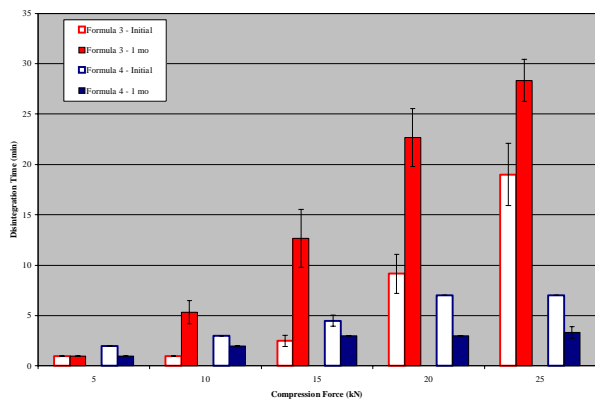


Figure 7. Tablet Disintegration Time – 1 Month



CONCLUSIONS

This study demonstrates that replacing lactose with Starch 1500® as an excipient would bring many benefits to tablet formulas designed for direct compression. It was found that self-lubricating Starch 1500® produced lower ejection forces compared to lactose, possibly preventing premature machine and tooling wear. The tablet hardnesses were higher with the lactose formula, but they were more than adequate with Starch 1500®. Press speed had little effect on these formulas. The disintegration times of the Starch 1500®-based formulas were dramatically lower than the lactose formulas at the higher compression forces.

This study also investigated tablet behavior on storage at elevated conditions. Despite the fact that Starch 1500® formulas produced tablets with lower mechanical strength compared to lactose 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 lactose in a formula would not only help to reduce stress on tooling, but would also benefit formulas through improved binding capability, improved disintegrant properties, and enhanced flow and lubricity.

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