MULTIFUNCTIONAL EXCIPIENTS

Choosing the right excipients can make all the difference in the efficient production of robust tablets. This article presents a case history of a pharmaceutical manufacturer that replaced a polymer binder, a super disintigrant and a portion of a standard filler with a multifunctional partially pregelatinized starch (PPG Starch) and achieved remarkable results. The PPG Starch improved the tablet's physical properties and dissolution properties with fewer processing steps, leading to a less complex formulation and dramatically lower costs. Gus Labella, Global Technical Manager Excipients, and Michael McDougal, Global Business Manager, Excipients, for Colorcon explain.

Today, more than ever, pharmaceutical formulators are seeking ways to improve the manufacturing process and product quality through the use of functional excipients.

Selecting the best excipients, however, is a juggling act, requiring a balance between time and cost efficiencies as well as anticipated product performance.

Historically, formulations in the development of new drug products contained native corn starch which was used as both a binder and disintegrant. As a binder, the starch was converted to a paste before adding it to the wet granulation. As a disintegrant, it was added dry to the powder blend. Due to flow and compressibility concerns, alternative excipients and excipient combinations were examined.

One such example is the use of polymer binders in combination with super disintegrants. Another is the use of PPG Starch.

The following case study demonstrates how a PPG starch, Starch 1500 from Colorcon, outperformed a polymer[1] and super disintegrant[2] in a high shear wet granulation application with an estimated cost savings of 60%.

One key reason is that Starch 1500 performs multiple functions within a wet granulation formulation, as a binder, disintigrant, filler and lubricant, eliminating the need for a multitude of costly excipients and additional processing steps.

Choosing excipients in wet granulation

High shear wet granulation is a preferred manufacturing method in many companies because it allows for rapid production of compressible granulations.

As stated, PPG Starch combines all the beneficial properties of both native corn starch and fully pregelatinized starch making it ideal as both a binder and disintegrant, eliminating the cost and time of separate products and processing steps.

Starch 1500 also has self-lubricating properties, which reduces the need for high levels of lubricants, thus improving mechanical strength and dissolution of the product.

Polymers such as PVP (povidone) can be used as binders, but require the addition of a super disintegrant.

When hydrated, these binders produce viscous, tacky, aggressive solutions

that hold the granules together, but can cause processing difficulties such as rapid over-granulation.

On stability, polymers can lead to tablet hardening and a decrease in dissolution performance, and since they typically require the addition of costly super disintegrants to break apart the tablet and granulation, the formulations are considerably more expensive, and can potentially have a negative effect on product stability as well as on the film coating appearance of the finished product.

In this case study, a pharmaceutical manufacturer wanted to accelerate the development process and reduce the overall cost of one of its products. The company used PVP, CCS (crosscarmellose sodium), MCC (microcrystalline cellulose) and magnesium stearate (see table I, Formula 1) as its initial formulation.

They sought a partner, Colorcon, with full-service capabilities to meet this formulation challenge – to accelerate the development process and reduce overall costs.

Colorcon created a formula, utilizing a water-soluble, high-dose model drug (Guaifenesin), with Starch 1500 (Formula 2) as both the granulation binder and the disintegrant. The pharmaceutical company compared the high shear granulation and tablet properties of the original formulation (Formula 1) with the new PPG Starch based formulation.

Results

Tablet hardness and friability

The PPG Starch based formula produced more robust tablets, with higher hardness in the upper range (see Figure 1). The use of stearic acid allowed for better bonding of materials. In addition, for nearly every compression force, Formula 2 produced lower friabilities (Figure 2). These are important benefits because more robust tablets enable the product to withstand further manufacturing steps such as film coating, printing, and packaging.

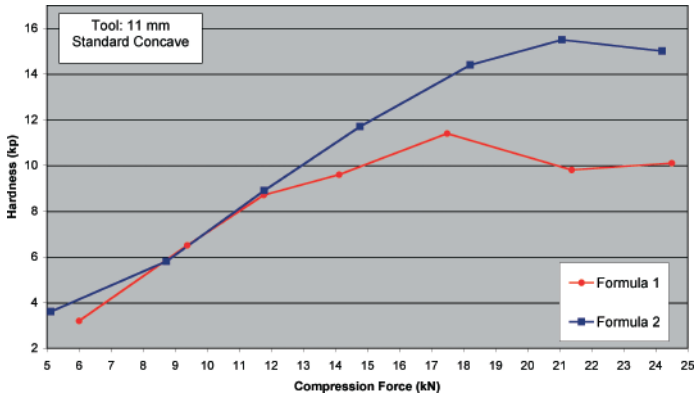

Figure 1: Tablet hardness

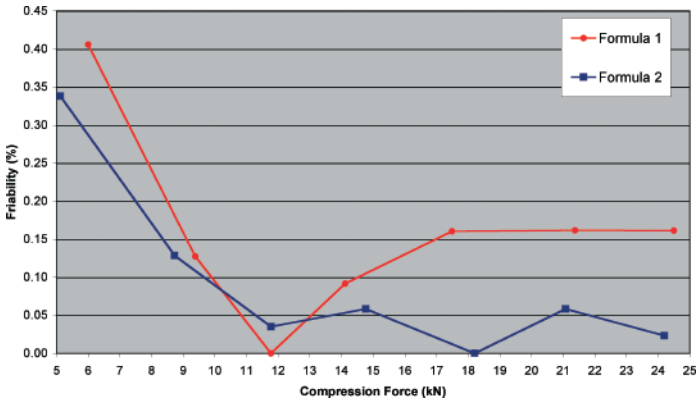

Figure 2: Tablet friability

Dissolution and disintegration performance

At all compression forces tested, disintegration times for Formula 2 were faster than those for Formula 1 containing a super disintegrant (Figure 3) even though the tablets in the upper compression force range were higher in hardness than Formula 1.

The PPG Starch based formula also produced a more rapid release of the drug (Figure 4). The tablets were compressed at the same force, 12 kN, and produced similar hardnesses. In addition, the PPG Starch formula produced a lower vessel to vessel variation in the percent of drug released at the 15 minute time point than Formula 1.

Ejection forces

Both formulations demonstrated effective lubrication with low ejection forces. Formula 1 was prepared with a common use level of magnesium stearate (1.0%) and due to the self lubrication properties of Starch 1500, Formula 2 required a lower level of lubricant while still producing satisfactory ejection forces.

Cost savings

The multifunctional Starch 1500 not only demonstrated performance benefits over polymer/super disintegrant combinations, but also improved cost-savings and profitability.

By replacing PVP, CCS (both generally higher priced excipients) and half of the MCC with the mutifunctional Starch 1500, the company achieved a substantial reduction in the raw material cost as well as in the cost of manufacture.

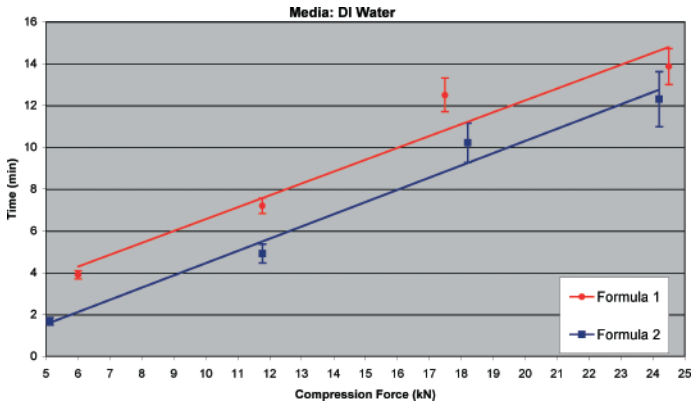

Figure 3: Tablet dissolution

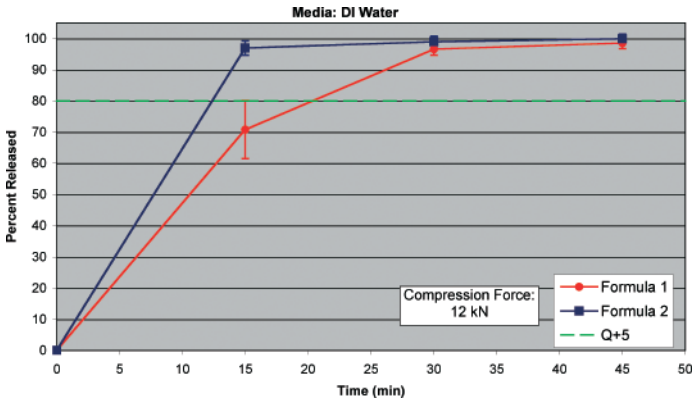

Figure 4: Tablet disintegration

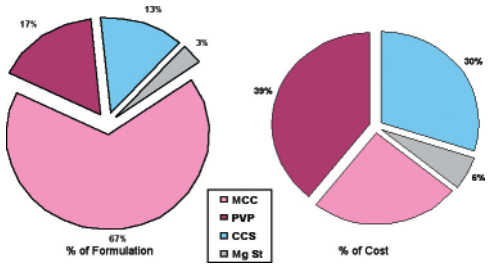

Figure 5: Cost Pie-chart

Table I: Recipe for Tablet Formulation

	Formula 1		Formula 2	
Ingredient	**Per cent**	**mg/tablet**	**Per cent**	**mg/tablet**
Granulation				
Guaifenesin USP	69.77	300	67.99	300
MCC NF	10	43	-	-
CCS NF	2	8.6	-	-
Povidone USP	5	21.5	-	-
Pregelatinized Starch NF	-	-	16	68.8
Dry additions				
MCC NF	10.23	44	9.48	40.77
CCS NF	2	8.6	-	-
Mag Stearate NF	1	4.3	-	-
Pregelatinized starch	-	-	4	17.2
Stearic acid NF	-	-	0.5	2.15
Colloidal Silicon dioxide NF	-	-	0.25	1.08
Total	**100**	**430**	**100**	**430**

Figure 5 shows that polymeric binders and super disintegrants can comprise up to 70% of the total excipient cost of a tablet. Replacing the PVP, CCS and half of the MCC with Starch 1500 can result in a formulation cost savings of more than 60%.

Conclusion

The study shows that Starch 1500 performed as an excellent binder, producing a compressible granulation and tablets with improved hardness and friability compared to a polymer and super disintegrant combination.

Overall, the Starch 1500 formula demonstrated excellent tablet properties and dissolution. While providing comparable binding, the Starch 1500 formula exceeded the disintegration and dissolution performance of the PVP formulation that included a super disintegrant. Formula 2 also showed lower vessel to vessel variation in dissolution compared to Formula 1.

Starch 1500 can be used in wet granulation, direct compression, capsule filling, and roller compaction formulations. The use of Starch 1500 is an excellent way to reduce process time and cost while preserving optimal properties in a well constructed formulation.

FOR MORE INFORMATION

For more information on Starch 1500® visit www.colorcon.com