Starch 1500®, Partially Pregelatinized Maize Starch, Used as a Binder Disintegrant in High Shear Wet Granulation Comparison to Povidone and Croscarmellose Sodium

INTRODUCTION

Historically, the majority of formulations in the development of new drug products contained native corn (maize) 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. Both methods were used frequently, because the starch lost much of its disintegration properties when it gelatinized in the preparation of the starch paste. As a dry addition to a granulation, the native corn starch did not flow well and was not very compressible.

Polymers

Today, polymers such as Povidone (PVP) are preferred as binders for wet granulated products. When hydrated, these binders produce viscous, tacky solutions. The tackiness holds the individual granules together. However, polymer binders can also lead to processing difficulties such as rapid over-granulation. Over time, they occasionally lead to tablet hardening and a decrease in dissolution performance.

Because a balance must be maintained between the binding and the disintegration properties of a formulation, when polymer binders are chosen, the addition of strong disintegrants, such as super disintegrants, are typically required. These materials surpass native corn starch in their ability to wick moisture and swell. However, super disintegrants are considerably more expensive and can have a negative effect on product stability as well as the film coating appearance of the finished product.

Current Processing Methods

High shear wet granulation is a preferred manufacturing method in many companies today. The high shear method allows for rapid production of compressible granulations. The resultant granulation characteristics depend on a combination of formulation properties and processing parameters. High- shear wet granulated products are typically dense due to the shear forces created during the high speed mixing in combination with the agitator blades. Polymers used in high shear wet granulation processing again require the addition of a disintegrant.

Using hot starch pastes as an alternative is not recommended because the introduction of heat can cause process variations. Cold pastes can be processed, but time is lost while waiting for the pastes to cool thus negating the benefits of the high shear functionality.

Pregelatinized Starch Alternatives

An alternative to native corn starch or polymers for wet granulations is pregelatinized starch. This is a starch that has been previously gelatinized and dried to powder form.

Functionally, pregelatinized starches are split into two groups, fully pregelatinized and partially pregelatinized. Fully pregelatinized starches are being used as binders in wet granulated formulations. But due to the gelatinization, much of the disintegration properties are lost. Partially pregelatinized starches on the other hand, have a mixture of properties of both native and fully gelatinized starches. This makes them useful as both a binder and a disintegrant in wet granulated formulations. High shear wet granulation is also well suited for the use of partially pregelatinized starches.

Partially pregelatinized starches can be hydrated with cold water to produce viscous slurries or, alternately, can be added directly to the granulator bowl and water can be utilized to granulate.

STUDY OBJECTIVES

This study compares the high shear granulation and tablet properties of two formulations. One is based on a polymer granulation binder, PVP, in combination with a super disintegrant, croscarmellose sodium (CCS). This formulation was developed external to Colorcon. The other formulation utilized partially pregelatinized maize starch, Starch 1500, as both the binder and the disintegrant.

MATERIALS AND METHODS

Table 1 lists the formulations evaluated for this study. The grades and sources of the materials follow: guaifenesin USP (Delta Synthetic Co), microcrystalline cellulose NF intragranular (EMCOCEL 50M; JRS Pharma), microcrystalline cellulose NF extra-granular (EMCOCEL 90M; JRS Pharma), croscarmellose sodium NF (Ac-Di-Sol; FMC BioPolymer), povidone USP (Kollidon 30; BASF), magnesium stearate NF (Mallinckrodt), pregelatinized starch NF (Starch 1500; Colorcon), colloidal silicon dioxide NF (CAB-O-SIL M-5P; Cabot), stearic acid NF (Oleotec).

The granulation process was carried out in a TK Fielder PMAT-10 (Niro Inc). The batch size was maintained at 2.0 kg for each trial. Materials were pre-blended for two minutes prior to granulating with an impeller speed of 300 RPM and chopper speed setting of II. Moisture content of the pre- blended ingredients was measured by loss on drying (LOD) with an Ohaus moisture balance at a temperature of 75°C. Granulation was performed by adding povidone solution or water to the granulator while mixing with an impeller speed of 300 RPM and a chopper speed setting of I. Each granulation batch used the same quantity of water to granulate, theoretically, 21% or 525 mL. The granulating solution was added through a binary spray gun at a rate of 150 g/min and an atomization pressure of 5 psi. After the addition of the liquid, the batch was “worked” for three minutes with an impeller speed of 300 RPM and a chopper speed setting of II. Drying was done using a Glatt GPCG-3 fluid bed processor with an inlet of 50°C. Each batch was dried to a moisture content close to the pre-blend LOD measured earlier.

Final sizing of the granulations was performed by hand, using an 18 mesh screen. Lubricants were passed through a 60 mesh screen prior to blending. In addition, the colloidal silicon dioxide was passed through a 30 mesh screen along with the MCC. Blending was performed with a Patterson Kelley twin shell, four quart blender. All ingredients except the lubricant were blended for 10 minutes. The lubricant was added and blended for an additional 5 minutes. Particle size analysis was performed with an ATM Sonic Sifter under the following conditions: sample size 10 g ± 0.5 g, test time 5 minutes, amplitude 4, sift-pulse setting. The geometric mean particle sizes and standard deviations were determined by plotting the weight percent greater than a given diameter (on a probability scale) versus the log of the diameter and performing a linear regression. Bulk and tapped density was performed in accordance with USP 28 method 1.

Tablets were compressed on an instrumented (SMI), Piccola (Riva), 10 station, rotary compression machine fitted with 11mm round, standard concave tooling. For each formulation, a compression profile was generated covering 6 to 24 kN at a turret speed of 30 RPM. Tablet properties were evaluated after compression with an Erweka Multicheck using a sample size of 10 tablets. Friability was evaluated at 100 drops using an Erweka Friabulator. Disintegration times were measured according to USP 28 with an Erweka DT bath using deionized water; the median disintegration time was reported. Dissolution was performed according to USP 28 in DI water with an automated VanKel dissolution apparatus and the samples were analyzed by UV at a wavelength of 274 nm.

RESULTS AND DISCUSSION

In addition to film coating support, Colorcon provides formulation services to customers using Colorcon products. The work contained within this paper was driven by providing a comparative formulation for a customer. The polymer/super disintegrant formulation was derived from a similar customer formulation but with a different drug substance.

Guaifenesin, a water soluble, high dose drug, was chosen as a model drug for these experiments. Guaifenesin is difficult to granulate and melts at a low temperature. Formula 1 is listed in Table 1 and utilizes common granulation excipients. The quantity of each ingredient was chosen to be within the recommended use levels. The granulation contains microcrystalline cellulose (MCC) at approximately 20% both internally and externally to the granulation. MCC can lose some compactability when used in wet granulations, therefore, it is desirable to incorporate a portion of it externally to ensure good tablet hardness. The 90 micron grade of MCC was used externally. The dissolution performance of a granu- lated formulation can be improved using super disintegrants both internally and externally to the granulation. CCS is used at 4% of the formulation and was split equally between the phases. Magnesium stearate was used as the lubricant for this formulation at a level of 1%. This level may not always be warranted in most formulations but many times it is selected without optimization in order to avoid any potential ejection force issues during compression. Since these ingredient levels were not originally determined by Colorcon, they were not altered for this study.

Table 1.

	Formula 1		Formula 2	
Ingredient	**Percent**	**mg/tablet**	**Percent**	**mg/tablet**
Granulation				
Guaifenesin USP	69.77%	300.00	69.77%	300.00
Microcrystalline Cellulose NF	10.00%	43.00	-	-
Croscarmellose Sodium NF	2.00%	8.60	-	-
Povidone USP	5.00%	21.50	-	-
Pregelatinized Starch NF	-	-	16.00%	68.80
Dry Additions				
Microcrystalline Cellulose NF	10.23%	44.00	9.48%	40.77
Croscarmellose Sodium NF	2.00%	8.60	-	-
Magnesium Stearate NF	1.00%	4.30	-	-
Pregelatinized Starch NF	-	-	4.00%	17.20
Stearic Acid NF	-	-	0.50%	2.15
Colloidal Silicon Dioxide NF	-	-	0.25%	1.08
Total	100.00%	430.00	100.00%	430.00

Formula 2 was created using Starch 1500 as both the granulation binder and the disintegrant. Because Starch 1500 is a partially pregelatinized starch it maintains beneficial properties of both native starch and fully pregelatinized starch. Table 1 lists the ingredients for this formulation. All of the PVP and the CCS were replaced with Starch 1500. In addition, the internal MCC was also replaced with Starch 1500. The external CCS was replaced with Starch 1500, but at twice the level. Starch 1500 is an effective disintegrant but it is not a super disintegrant and typically needs to be used at higher levels to gain similar disintegration performance. The level in the external phase was 4%. The total Starch 1500 content in the formulation was 20%.

Magnesium stearate was replaced with stearic acid and colloidal silicon dioxide. Magnesium stearate can be detrimental to particle bonding in plastically deforming materials such as pregelatinized starch and MCC. Magnesium stearate is a more effective lubricant than stearic acid, therefore, when used at the same level, magnesium stearate should produce lower ejection forces than stearic acid. Since Formula 2 contained 20% Starch 1500, a reduced level of stearic acid was chosen because Starch 1500 also has self lubricating properties. The addition of colloidal silicon dioxide to the formulation is important when using stearic acid since it does not have anti-adherent properties. The inclusion of colloidal silicon dioxide, at half the level of the stearic acid, will keep product from adhering to the punch faces. The level of the external MCC was then adjusted in order to maintain the tablet weight of 430 mg.

Both granulations produced during this study were of acceptable quality. Tables 2 and 3 show the granulation properties.

Formula 1 produced a slightly denser granulation and also produced a larger mean particle size than Formula 2. This can be attributed to the difference between adding the binder in solution versus dry. When all of the binder is solubilized, there is greater binding strength.

Table 2. Granulation Densities

Product	Average Bulk Density	Average Tapped Density	Average Carr's Index
Unit	**g/cc**	**g/cc**	**%**
Formula 1	0.590	0.675	12.6
Formula 2	0.570	0.680	16.1

Table 3. Granulation Particle Size

Product	Granulation Geometric Mean	Geometric Standard Deviation	Final Blend Geometric Mean	Geometric Standard Deviation
Unit	**µm**	**NA**	**µm**	**NA**
Formula 1	194	2.28	169	2.64
Formula 2	178	2.37	144	2.47

Figure 1 shows the difference in geometric mean particle sizes of the raw granulations and the final blends. Since external ingredients are being added to the granulation, a shift in the mean particle size is seen.

Figure 1. Geometric Mean Particle Size

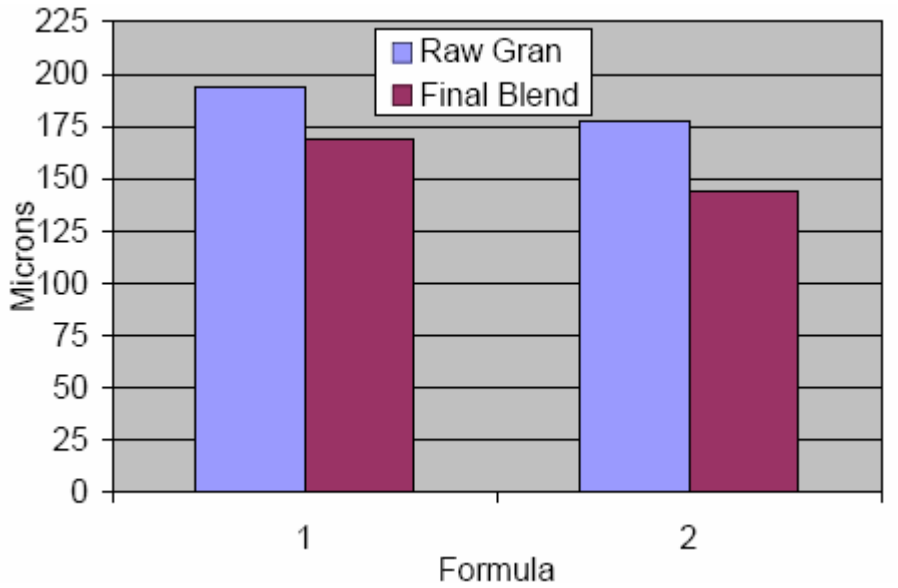


Table 4 lists the moisture content of the granulations at different points within the manufacturing process. Since Starch 1500 has a moisture content of approximately 9%, the pre- blend LOD for Formula 2 is slightly higher than Formula 1.

Table 4. Granulation Moisture Levels

Product	Pre-Blend LOD	Wet LOD	Gran. Final LOD	Final Blend LOD
Unit	**%**	**%**	**%**	**%**
Formula 1	0.4	14.7*	1.0	1.3
Formula 2	1.3	19.8*	1.6	2.0

*Some melting on moisture balance.

The compressibility of many pharmaceutical ingredients is sensitive to moisture content. The pre-blend LOD represents the natural moisture condition of the ingredients in the granulation prior to granulating. During development, a formulator would evaluate different drying endpoints in order to produce granulation moisture contents above and below the normal condition. These would then be evaluated to determine the impact on tableting performance. Each granulation batch used the same quantity of water to granulate, theoretically 21%. The data values for the wet LOD's are not valid due to melting and evaporation of the drug on the moisture balance.

In order to add the granulating fluid to the product, a spray gun was utilized with both formulations. Previous trials without utilizing a spray gun led to the creation of many small agglomerates in the granulator. Due to the aggressiveness of the PVP binder, if the solution was not atomized or dispersed finely, agglomerates formed as the solution contacted the dry powders. Depending on the number and size of these agglomerates, the batch may require wet milling prior to drying. When trials without a spray gun were run with Starch 1500 as the binder, no agglomerates were produced giving a more uniform granulation. This could save considerable manufacturing time by eliminating the need for wet milling.

Figure 2 displays the tablet hardness of the two formulations. Both produced tablets of similar hardness in the lower range of compression force. In the upper range, Formula 2 produced tablets of higher hardness than Formula 1. This formula, containing Starch 1500 and MCC, utilized a better choice of lubricant. Stearic acid allows for better bonding of these plastically deforming materials.

Figure 2. Compression Profile

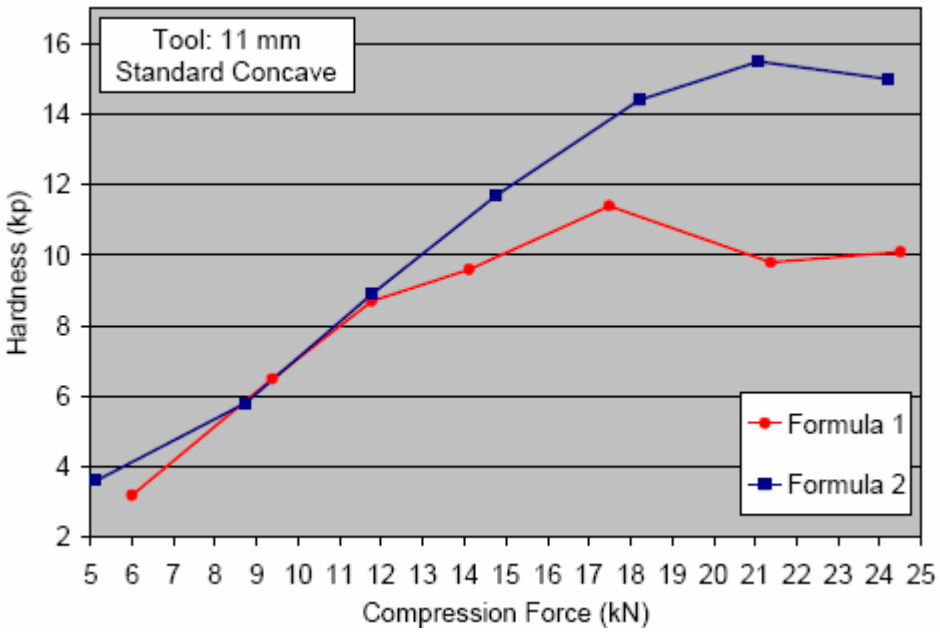


Figure 3 shows the friability profiles of the products. Again, both formulations produced similarly low friabilities. For nearly every point, Formula 2 produced lower friabilities than Formula 1. Tablets must be of sufficient hardness and have low friability in order to withstand further unit operations such as film coating, printing, and packaging.

Figure 4 plots the ejection forces for each formulation. Formulation 2, which used stearic acid, a less effective lubricant than magnesium stearate, produced slightly higher ejection forces than Formula 1. Stearic acid is commonly used at twice the level of magnesium stearate. Both formulations, however, provide effective lubrication with values less than 400 N being preferable on this tablet press.

Figure 3. Friability Profile

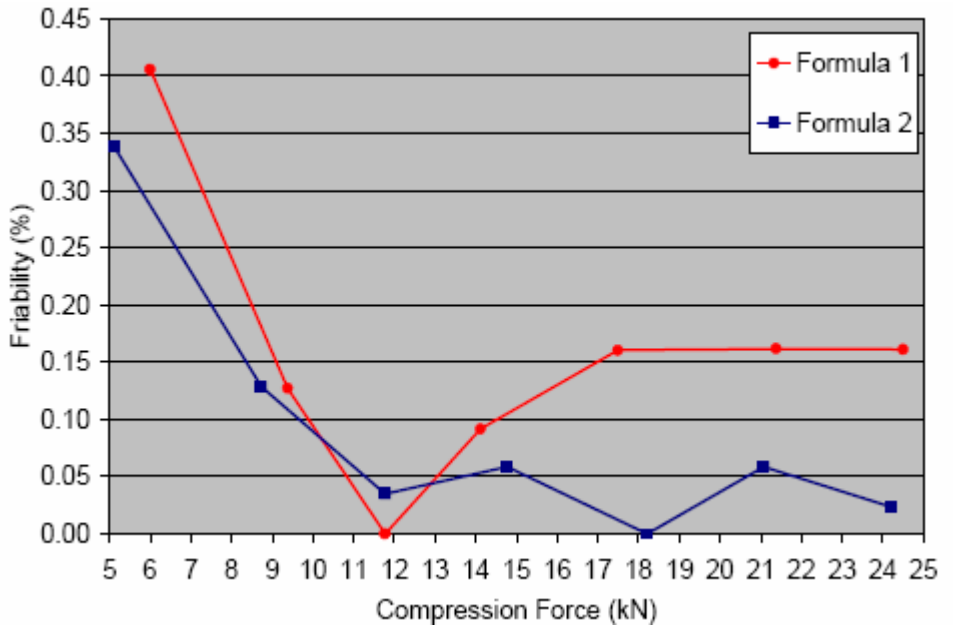


Figure 4. Ejection Profile

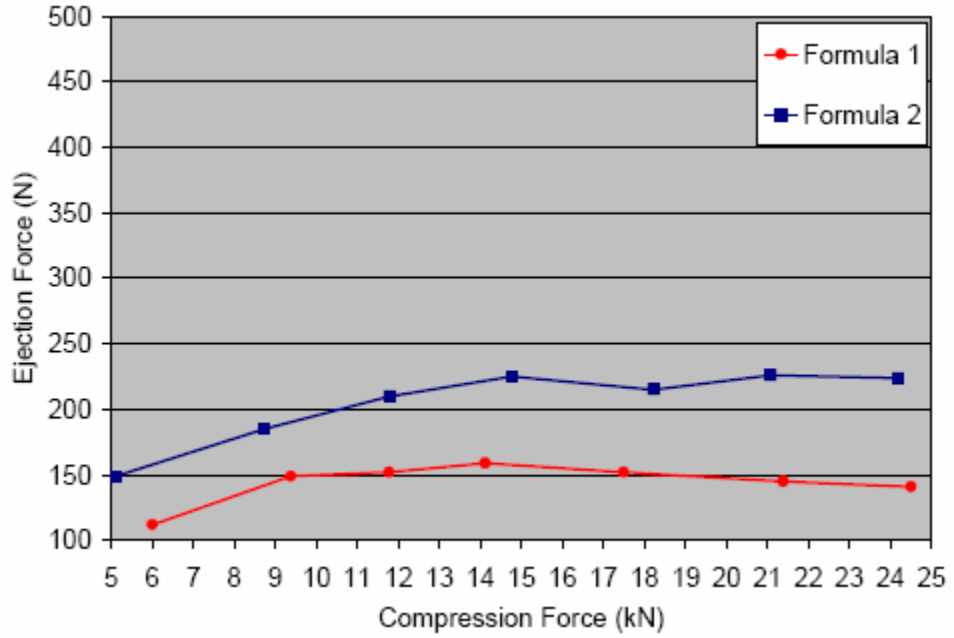


Figure 5 details the disintegration performance of the two formulations. At all compression forces tested, Formula 2 produced disintegration times that were lower than those for Formula 1 containing super disintegrant.

Figure 5. Median Disintegration Profile

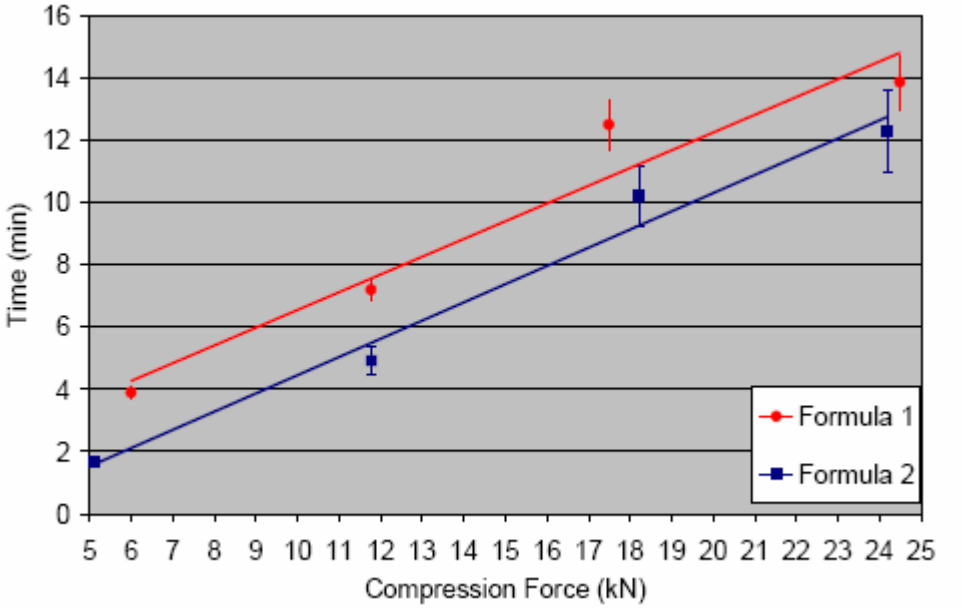
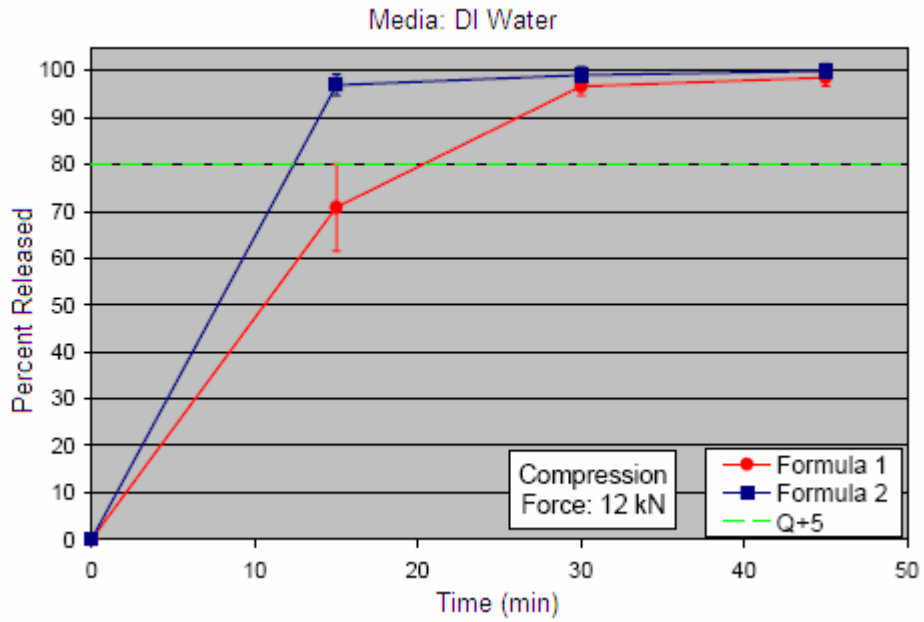


Figure 6 represents the dissolution data for both formulations. While both meet the USP specifications, Formula 2 produced a more rapid release of the drug. This is due to the inclusion of Starch 1500 in the formulation. In contrast to Formula 1, Starch 1500 performs not only as a binder but also is an effective disintegrant allowing the tablet to break down at a faster rate. Tablets used to produce dissolution data were compressed at the same force, 12 kN, and produced similar hardnesses. In addition, Formula 2 produced a lower vessel to vessel variation in the percent drug released at the 15 minute time point than Formula 1. Again, this is attributable to the use of Starch 1500 in the formulation. The distribution of Starch1500 in the tablets at 20% should be more uniform than 4% CCS.

Figure 6. Dissoultion

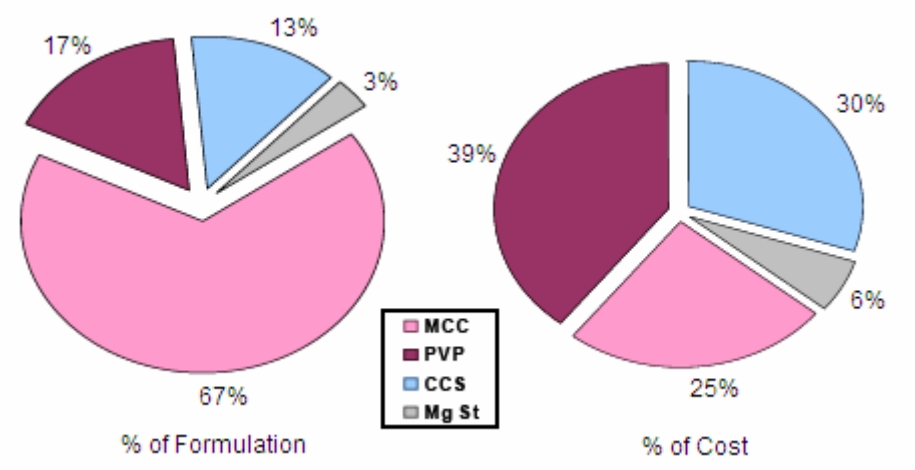


FORMULATION COST ANALYSIS

This study has illustrated the multiple properties of Starch 1500 and how it compares to a formulation containing PVP and CCS. As well as bringing performance benefits, Starch 1500 can increase the profitability of a formulation. By replacing the PVP and CCS, both expensive excipients, with Starch 1500, a substantial reduction can be achieved in the raw material cost as well as in the cost of manufacture.

Figure 7 is an excipient comparison for Formula 1 containing PVP and CCS. The figure shows the percentage of each excipient that make up the formulation and the associated costs by percentage. While MCC comprises 67% of the excipients, it only represents a small portion of the excipient costs. Together, the PVP and CCS represent nearly 70% of the excipient costs. If the povidone, croscarmellose sodium, and half of the microcrystalline cellulose are replaced with Starch 1500, a cost savings in excess of 60% can be realized.

Figure 7. Excipient Comparison – Formula 1



CONCLUSIONS

This study shows the multifunctional properties of Starch 1500 in a high shear wet granulation application. Starch 1500 performed as an excellent binder producing a granulation that was compressible and produced tablets of improved hardness and friability compared with those prepared with PVP. While providing comparable binding, the Starch 1500 formulation exceeded the disintegration and dissolution performance of the PVP formulation which utilized super disintegrant. The use of Starch 1500 in the formulation showed lower vessel to vessel variation in dissolution than Formula 1 using CCS. In addition, PVP and super disintegrants may have a negative effect on the film coating process and product stability, especially for moisture sensitive drugs.

This study has shown that Starch 1500 can produce beneficial results while reducing the overall cost and complexity of a formulation. Starch 1500 can be added directly to the granulator bowl eliminating the need to prepare a binder solution. Also, it was shown that lubricant choices and levels can impact product performance. Ingredients and levels should be justified with data in each formulation.

Starch 1500 also has high density and good flow properties and can be used in wet granulation, direct compression, and capsule formulations. In conclusion, using Starch 1500 is an excellent way to reduce process time and cost while preserving optimal properties in a well constructed formulation.

For more information, contact your Colorcon representative or call:

North America	Europe/Middle East/Africa	Asia Pacific	Latin America
+1-215-699-7733	**+44-(0)-1322-293000**	**+65-6438-0318**	**+54-11-4552-1565**

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