# Evaluation of Partially Pregelatinized Starch in a Continuous High Shear Wet Granulation Process

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## Introduction

High dose, poorly compressible active pharmaceutical ingredients (API) may not be suitable for continuous direct compression applications and may require an additional wet granulation and drying step prior to compression. Twin screw granulation (TSG) provides an effective means of subjecting API and excipients to the high shear necessary for granulation and allows for a continuous mode of operation within a continuous manufacturing process. Partially pregelatinized starch (PPS) is comprised of native unmodified starch and fully gelatinized starch fractions. PPS can be hydrated with cold water to produce viscous slurries or added directly to the granulation mix with a simple addition of water to granulate. The unmodified native starch fraction of PPS will remain intact throughout the cold-water granulation process and provide disintegration properties to the final dosage form1. The objective of this study was to evaluate the feasibility of using PPS to provide binder and disintegrant properties to a high dose TSG formulation. A comparative formulation using a polymeric binder, polyvinylpyrrolidone (PVP), was also evaluated.

## Methods

Acetaminophen powder USP (APAP, Mallinckrodt) was chosen as the model API for the study, due to its poor powder flow and low compressibility. The trial formulation contained 83.3% w/w APAP, 16.4% PPS (Starch 1500®, Colorcon Inc.) and 0.25% magnesium stearate (Peter Greven) in an extra granular addition. A second formulation contained a reduced level of PPS (11.4%) and of 5.0% PVP (Kollidon® 30, BASF) (Table 1).

**Table 1. Composition of the APAP Formulations**

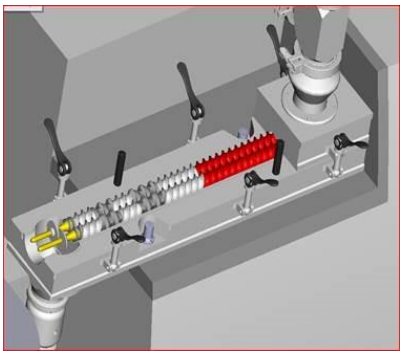
| Ingredient | Formulation 1a (%) | Formulation 1b (%) | Formulation 2a (%) | Formulation 2b (%) |
|---|---|---|---|---|
| APAP | 83.33 | 83.33 | 83.33 | 83.33 |
| Starch 1500 | 16.42 | 16.42 | 11.42 | 11.42 |
| PVP | 0 | 0 | 5 | 5 |
| Mg. stearate | 0.25 | 0.25 | 0.25 | 0.25 |
| Water (5) * | 30 | 15 | 15 | 10 |

**water used for continuous granulation process, evaporates during drying stage*

APAP and excipients (except Mg. stearate) were dry blended prior to the TSG process. The feeding, wet granulation and drying processes were conducted using a ConsiGma™-1 (GEA Pharma Systems) as shown in Figures 1 and 2.

**Figure 1. ConsiGma-1 Processor**

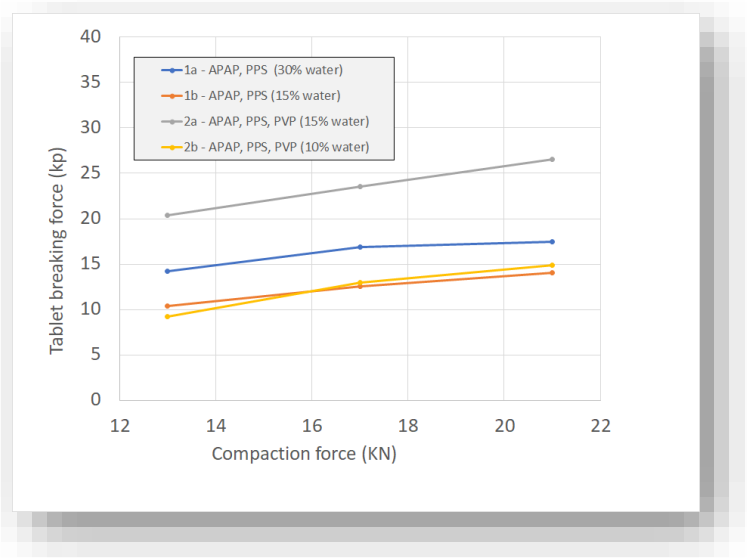
**Figure 2. ConsiGma-1 TSG Configuration**



## Results

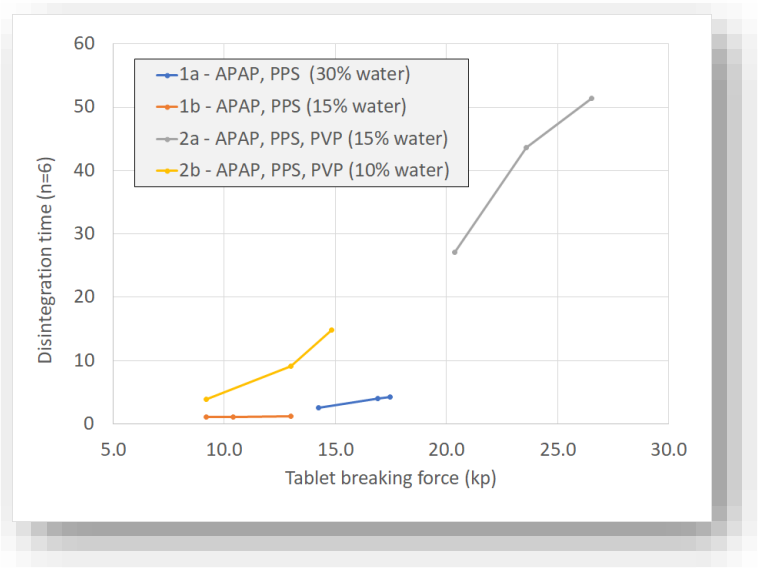
Both formulations, with or without PVP, and at varying water addition levels, produced free-flowing granules and robust tablets. It was found that increased water addition levels during granulation resulted in higher overall tablet hardness; this effect was especially pronounced with formulations 2a and 2b, containing PVP (Figure 3).

**Figure 3. Compaction Profiles of APAP Formulations**



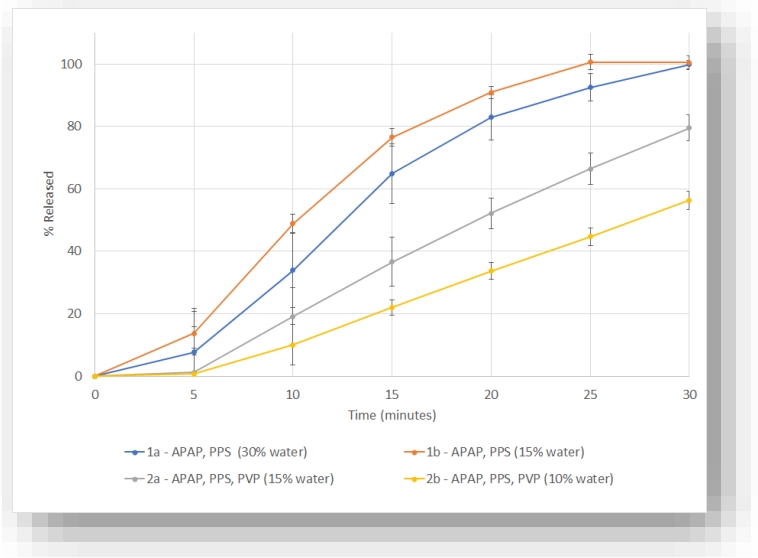

The formulations 1a and 1b containing only PPS, exhibited faster disintegration times (<5 minutes) irrespective of water addition levels, compaction force or tablet hardness. Formulations 2a and 2b with PVP, exhibited high sensitivity to water addition, compaction force and tablet hardness with resulting disintegration times ranging from 5 to 51 minutes (Figure 4).

**Figure 4. Tablet Disintegration Time Vs. Breaking Force**




Drug release was rapid for the formulations with PPS alone, irrespective of water addition levels or tablet hardness, whilst the formulations containing PVP failed the USP release criteria of >80% released in 30 minutes (Figure 5).

**Figure 5. Dissolution Profiles for Tablets with Breaking Force of 13kp**




The coated tablets for all formulations were smooth and defect free (Figure 6) and film coating had no impact on drug release.

**Figure 6. Film Coated APAP tablets**

## Conclusions

This study indicated that Starch 1500 (PPS) can provide effective binding and disintegrant properties to a high dose, poorly compressible API in twin screw wet granulation applications. PPS simplified the formulation and increased the efficiency of continuous processes by reducing or eliminating the need for other excipients such as superdisintegrants. The ConsiGma™-1 processer allowed for rapid screening of granulation conditions with parameters that are directly transferable to the ConsiGma™ CTL Continuous Tableting Line.

## References


1. Wet Granulation of Acetaminophen with Starch 1500, Technical data sheet https://www.colorcon.com/products-formulation/all-products/102-starch-1500/126-wet-granulation-of-acetaminophen-with-starch-1500 accessed April 2019





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