# Evaluation of Pre-lubricated Co-processed Excipients for Use in High Speed Tabletting Operations

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## Introduction

In recent years, many new co-processed excipients have been launched to assist formulators with achieving more consistent performance and delivery characteristics, as well as to meet the industry challenges for faster, more consistent production. Most of these excipients are combinations of traditional fillers, binders, or disintegrants designed to improve physical properties. Co-processing while maintaining the individual chemical identity of each excipient was identified as the ideal method for creating improved excipients for the same reasons that wet granulations are performed. Granulating the ingredients together creates an improvement in flow, particle size, and uniformity when compared to dry blends of the same ingredients. In either case of wet granulation or co-processed excipient systems, there still remains a necessity to add a lubricant, such as Magnesium Stearate to the mix prior to tabletting. The lubricant prevents sticking of tablets to the tablet press and reduces chipping and capping, unfortunately it also diminishes some of the very benefits that wet granulation or co-processing provide. This is because Magnesium Stearate is very fine and dusty, does not flow well, leaves residue on equipment and is hard to clean. It can also coat over disintegrants or binders, leading to increased dissolution times and decreased tablet hardness. Consequently, granulation of Magnesium Stearate with other ingredients generally creates adverse formulation issues. Nonetheless, it would follow that co-processing with the right technology while enhancing the performance of another common, more stable lubricant could create the ideal performance characteristics while maintaining the consistent quality properties generally associated with granulating or co-processing. Such an excipient would also be ideal for addressing the challenges of new, even higher speed tabletting operations.

Three new co-processed excipients have been developed that combine a lubricant with a compression aid, allowing for the blending of the API, followed by tabletting, without a final lubricant blend step. Each of these three products are based on one of the following widely used compression aids, Anhydrous Lactose, Spray Dried Lactose, and Microcrystalline Cellulose, all of which are co-processed with Glyceryl Monostearate as the lubricant. The three products are called LubriTose™ AN (Anhydrous Lactose/Glyceryl Monostearate), LubriTose™ SD (Spray Dried Lactose/Glyceryl Monostearate), and LubriTose™ MCC (Microcrystalline Cellulose(MCC)/Glyceryl Monostearate). The lubricant is co-processed in a manner that allows for a thin coat of lubricant over the particles that allows for sufficient lubrication, even after addition of API.

The products will be evaluated to determine if co-processing with the lubricant results in physical improvements in the excipients and also to the final formulation after API addition. The properties that will be evaluated include the following:

- Flow properties of the co-processed excipient compared to physical blends with Magnesium Stearate
- Lubrication properties of the co-processed product compared to physical blends with Magnesium Stearate
- Flow properties of final formulations with API compared to physical blends with Magnesium Stearate
- Tablet weight uniformity at various press speed using LubriTose™ products compared to physical blends with Magnesium Stearate

In high speed tabletting operations, these are the properties, that when optimized, can lead to faster speeds with less tablet uniformity issues.

## Materials & Methods

The following co-processed products from Sheffield Bio-Science will be evaluated: LubriTose™ AN, LubriTose™ SD, and LubriTose™ MCC. The materials for the physical blends used for comparison are Anhydrous Lactose (Sheffield Bio-Science), Spray Dried Lactose 316 (Foremost Farms), MCC 212 (Ming Tai), and Magnesium Stearate (SD Chemicals). API's were obtained from VWR or Sigma Aldrich.

**Blending.** Powders were blended using V-shell blenders, with a blend time of 15 minutes for all ingredients except for Magnesium Stearate, which is blended in a final step for 5 minutes. For flow testing of just excipients, LubriTose™ products were compared to physical blends of the compression aid and magnesium stearate (0.5%). For lubrication studies, LubriTose™ products were compared to physical blends of the compression aid and magnesium stearate (0.5%). For flow testing with an API, LubriTose™ products were blended with the API for 15 minutes and compared to physical blends of the compression aid blended with the API for 15 minutes and then blended with magnesium stearate for 5 minutes. For tablet weight uniformity at various press speeds, LubriTose™ products were compared to physical blends of the compression aid and magnesium stearate (0.5%).

**Powder flow.** Powder flow testing was performed by measuring angle of repose and Carr's index. Carr's index was calculated by the following formula: (tapped density – bulk density) x 100 / tapped density. A lower Carr's index equals better flowability.

## Results & Discussions

**Product composition.** Three products were designed to offer the user a choice between using Anhydrous Lactose, Spray Dried Lactose, or MCC as the compression aid. Each one was co-processed with the Glyceryl Monostearate (GMS) using a Sheffield Bio-Science proprietary process enable even distribution of the GMS onto the compression aid.

**Table I: Product Compositions**

| Product | Co-processed Ingredients | % in Formula |
|---|---|---|
| LubriTose™ AN | Lactose Anhydrous | 96 |
| | Glyceryl Monostearate | 4 |
| LubriTose™ SD | Lactose Spray Dried | 96 |
| | Glyceryl Monostearate | 4 |
| LubriTose™ MCC | Microcrystalline Cellulose | 98 |
| | Glyceryl Monostearate | 2 |

**Flow properties of LubriTose™.** With angle of repose, LubriTose™ AN and LubriTose™ MCC had a lower angle of repose than the physical blend, meaning better flowability. LubriTose™ SD was the same as the physical blend. That is because spray dried lactose flows very well to begin with, and even after the addition of magnesium stearate. With Carr's index, all three LubriTose™ products had a lower value than the physical blend. The values were all less than 20, indicating good flowability. The physical blend of spray dried lactose/magnesium stearate was also less than 20 but the physical blends with anhydrous lactose/magnesium stearate and mcc/magnesium stearate were both over 20.

**Table II: Flowability Data of LubriTose™ Products Compared to Physical Blends**

| Product | Angle of Repose | Carr's Index |
|---|---|---|
| LubriTose™ AN | 41 | 17.3 |
| Physical Blend | 45 | 22.2 |
| LubriTose™ SD | 34 | 15.9 |
| Physical Blend | 34 | 16.7 |
| LubriTose™ MCC | 42 | 18.5 |
| Physical Blend | 50 | 23.8 |

**Lubrication properties.** The lactose based LubriTose™ products contain 4% GMS, while the MCC LubriTose™ contains 2%. These amounts were chosen so that when they are diluted with a high percentage of API, there is enough lubricant to provide adequate lubrication, but, when used nearly alone with a low percentage of API, they remain compressible. These amounts in theory represent the values that give the widest range for dilution since, when used at 50%, for example, there is 2% lubricant available. This may be more than typical with magnesium stearate, but that is added in the last step after API addition, where with LubriTose™, its added prior to API addition so slightly more lubricant may be necessary. This, of course depends upon the API properties, but was tested in Figures 1 and 2. Figure 1 represents LubriTose™ AN alone compared to Lactose and magnesium stearate at 0.5%. Of course LubriTose™ provides better lubrication since there is 4% GMS. In Figure 2, however, LubriTose™ is compared straight, and then diluted with API at 25, 50, and 75% levels and then compared to lactose magnesium stearate at 0.5% (this has 50% API, but it is not significant as the magnesium stearate is added at the end). It was observed that as expected, straight LubriTose™ provided the lowest ejection force and when diluted with 50% API (so 2% GMS), it was nearly equal to the lactose and magnesium stearate formula. At only 25% LubriTose™ (1% GMS), the ejection force was slightly higher than the magnesium stearate formula. This verifies that LubriTose™ can be used at various levels in the formula, even down to 25%, and still provide comparable lubrication to formulas with magnesium stearate. The same would be expected of LubriTose™ SD and LubriTose™ MCC.

**Figure 1**: Ejection force versus compression force profile for LubriTose™ AN and a physical blend of lactose anhydrous and magnesium stearate.

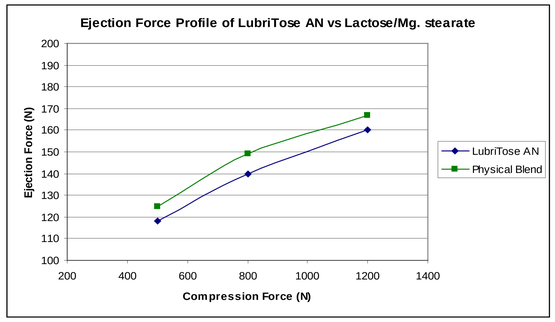
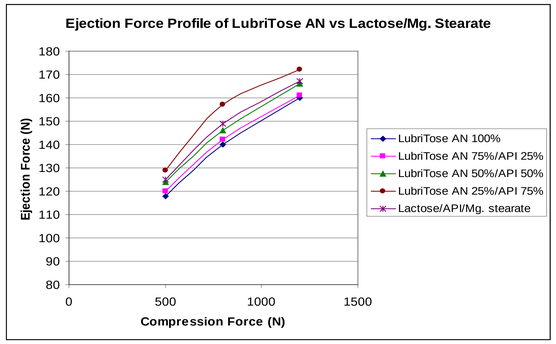



**Figure 2**: Ejection force versus compression force profile for LubriTose™ AN blended with various API levels and a physical blend of lactose anhydrous, API, and magnesium stearate.




**Flow properties of final formulations.** For this study, the flow properties of formulations using LubriTose™ AN and LubriTose™ MCC were compared to physical blends. LubriTose™ SD was not studied, since the flow of spray dried lactose is very good to begin with. Four APIs were used in these formulas and blended with either LubriTose™ or a blend of compression aid and magnesium stearate, Ibuprofen, Baicalein, Aspirin, and Mefenamic Acid. The amount of API in the formulas is as follows, Ibuprofen (80%), Baicalein (20%), Aspirin (50%), and Mefenamic Acid (50%). Carr's index was then calculated for the LubriTose™ formulations and the physical blends. The results in Figures 3 and 4 indicate that for all formulas tested, the Carr's index was lower in the LubriTose™ versions. There was also a large improvement in the LubriTose™ MCC formulas compared to the physical blends.

**Figure 3**: Carr's index of formulations with LubriTose™ AN and API compared to anhydrous lactose, API, and magnesium stearate.

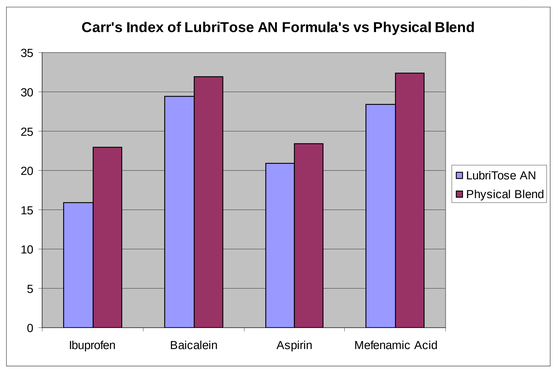
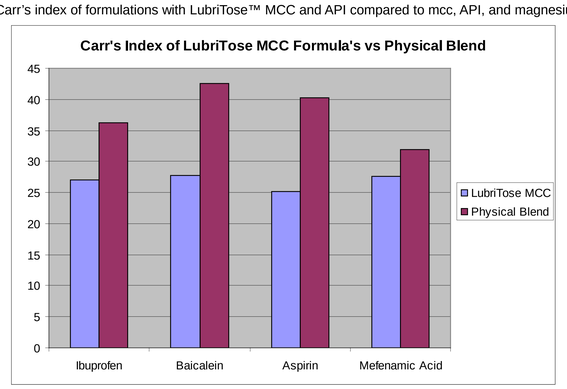



**Figure 4**: Carr's index of formulations with LubriTose™ MCC and API compared to mcc, API, and magnesium stearate.




**Tablet weight uniformity at increased press speed.** Due to the improvement in flowability of LubriTose™ formulations over physical blends, these formulations should be optimal for operating at high tablet press speeds. In Figures 5 and 6, LubriTose™ AN and MCC were compared to physical blends once again but at increasing press speeds. LubriTose™ SD was not compared since the flow of spray dried lactose is very good to begin with. The testing was completed at press speeds of 25, 50, and 75 rpm's. At each speed, ten random tablets were collected, weighed, and the average calculated. No adjustments were made to the fill weight as the speed was increased. As observed in the figures, with LubriTose™ formulations, the average tablet weight slightly decreased with increasing press speed. With the physical blends, the decrease in average tablet weight was more pronounced. The tablet press fill weights could be adjusted, but as observed, only minor adjustments would be necessary with the LubriTose™ formulations. This may result in a more robust process where adjustment may not even be necessary.

**Figure 5**: Average tablet weights of LubriTose™ AN formulas compared to anhydrous lactose and magnesium stearate at increasing press speeds.

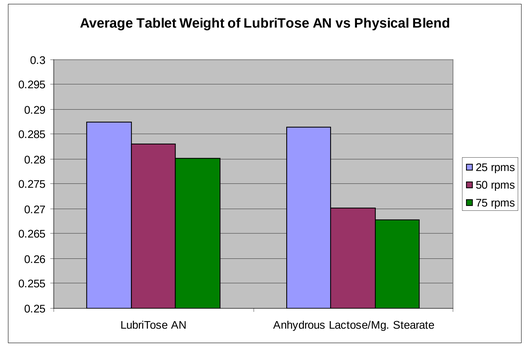
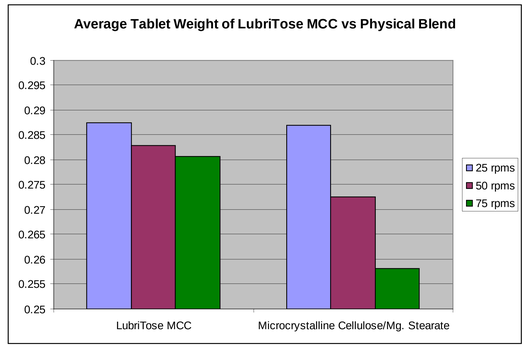



**Figure 6**: Average tablet weights of LubriTose™ MCC formulas compared to mcc and magnesium stearate at increasing press speeds.




## Conclusions

The LubriTose™ line of excipients are co-processed systems designed to enhance the performance of the individual components. They consist of a compression aid (Anhydrous Lactose, Spray Dried Lactose, or Microcrystalline Cellulose) co-processed with Glyceryl Monostearate as a lubricant. The ingredients and the co-processing process were chosen to create optimized performance characteristics, such as product flow, lubrication capacity, and final formulation tablet uniformity compared to physical blends of traditional ingredients. The objective of the study was to evaluate and substantiate these benefits.

A substantial benefit in flowability was observed in all three LubriTose™ products compared to the physical blends of excipients. This was as expected due to the co-processing technology used to create granules from the relatively poor flowing powders.

Lubrication was also evaluated since the products are co-processed using a tablet lubricant from vegetable origin. Even after co-processing, the ejection force was lower with tablets made from LubriTose™ compared to physical blends. However, with LubriTose™, since the lubricant is co-processed in, the API addition occurs after the lubricant has been added. In contrast, with physical blends, all of the ingredients including the API are blended, and the lubricant added at the end of the process. This is also necessary with the use of Magnesium Stearate due to the potential for overblending that can result in rejections. Lubrication studies were performed to determine if LubriTose™ would provide enough lubrication even after the addition of API. The ejection force when using LubriTose™ was similar to physical blends even when the formula contained only 25% LubriTose™ and 75% API. This verifies that even though API is added to the pre-lubricated product, there is enough available lubricant to provide excellent lubrication capacity. In addition, even at extended blend times of up to two hours beyond the standard time, no overblending issues were observed with LubriTose™ and tablets exhibited the same characteristics.

Final tablet formulations using typical poorly flowable API's were also tested to determine if LubriTose™ could improved the flow in the final formulation as compared to physical blends. In all cases, the final formulations had better flow in the LubriTose™ versions than the physical blends.

Lastly, tablet weight uniformity at increasing press speeds was compared for LubriTose™ tablets versus the physical blends. The average weight of the tablets with physical blends dropped dramatically whereas with LubriTose™ the difference was clearly negligible. This demonstrates that LubriTose™ formulas are more robust, have improved content uniformity at high speeds and will dramatically reduce the necessity for equipment adjustments during high speed tabletting.
Clearly, the extensive testing substantiated the benefits of using LubriTose™ versus physical blends of traditional ingredients relative to high speed flow characteristics, lubrication capacity, and tablet weight uniformity, properties known to be important in high speed tabletting operations.