LubriTose™

Self Lubricating Excipients

Shifting paradigms in tablet manufacturing

KERRY

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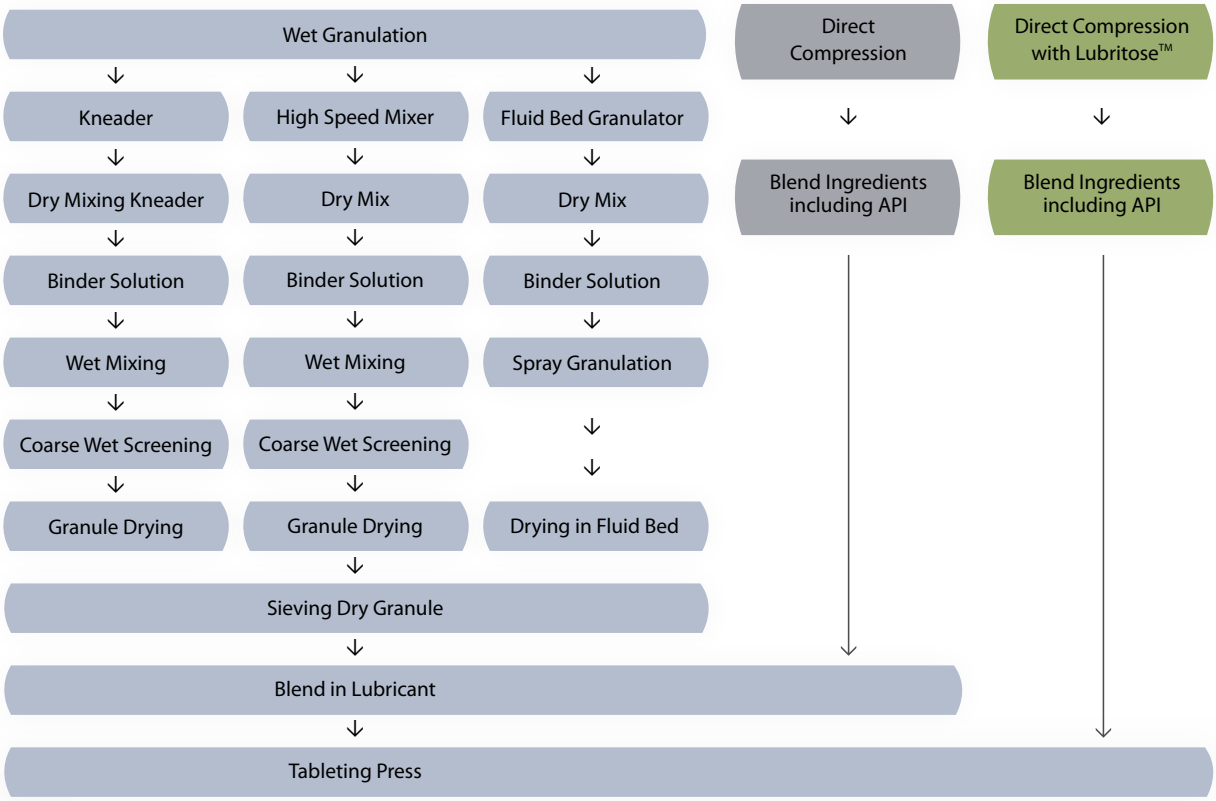
Simplifying the Tabletting Process

Direct compression was developed in the mid-1960s to simplify the costly and complex wet or dry granulation methods of tabletting. In the direct compression method of tablet production, dry ingredients are thoroughly mixed and then compressed into tablets. This eliminates the wetting and drying steps associated with the wet granulation method. Wet granulations are also costly because the additional steps require more equipment, and also increased costs for labor, validations and testing, and energy. As a result, direct compression is a quicker, more economical method that is widely used in the production of high quality tablets. However, with direct compression and also wet granulation, a lubricant is added in the last blending step to prevent tablets from sticking to the tablet press tooling. Without the lubrication step, tablets would stick leading to defects such as capping or picking.

LubriTose™ simplifies the tabletting process even further by eliminating the need for adding a separate lubricant to a formulation. The lubricant is co-processed onto the compression aid, eliminating the need for a separate lubrication blending step.



Self Lubricating Excipients

The LubriTose™ line of excipients are integrated co-processed systems designed for direct compression, high speed tabletting operations. Co-processing the directly compressible binding agent with a lubricant enhances the performance of the individual components while eliminating the limitations typically encountered with using Magnesium Stearate as a lubricant. The ingredients and the co-processing process were selected to create optimized performance characteristics, such as product flow, lubricity, and final formulation tablet uniformity compared to physical traditional blend of an excipient and lubricant.

LubriTose™ is available as Anhydrous Lactose, Spray Dried Lactose, Microcrystalline Cellulose (MCC) , or mannitol as a 'base' excipient.

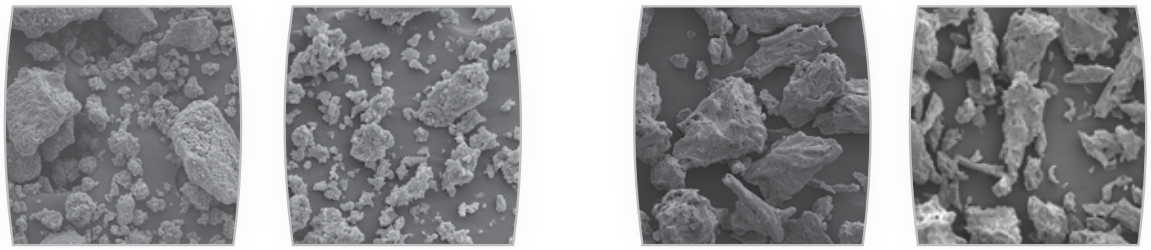
CO-PROCESSED INGREDIENTS – TYPICAL LEVELS		
Lactose NF/EP/JP (96%) Glyceryl Monostearate NF (4%)	Mannitol NF/EP/JP (96%) Glyceryl Monostearate NF (4%)	Microcrystalline Cellulose NF/EP/JP (98%) Glyceryl Monostearate NF (2%)

Note: There is not a monoglyceride monograph for EP/JP

Advantages

- Less processing steps
- Eliminates need for external lubricant and time sensitive blending
- Improve flow & tablet weight uniformity
- No impact on compression or API dissolution

LubriTose™ | LubriTose™ MCC



LubriTose™ (lactose) | Anhydrous Lactose | LubriTose™ (MCC) | Microcrystalline Cellulose

LubriTose™ has less rounder, smoother particles and less fines due to the agglomeration which equates to less dusting and better flow

LubriTose™ Application Data

In recent years, excipinet manufacturer and equipment manufacturers alike, have tried to find ways to eliminate the need to add external lubricants to the powder blend, prior to tabletting. The problems of using Mg St as a lubricant are well documented. However, by combining an alternaitve lubircant (GMS) intimately in to a 'base' excipient from the very beginning, we have been able to develop directly compressible excipients, that are essentially self-lubricating. Along with that, we found additional benefits were also apparent such as improved flow, and less tablet weight variation, even at high turret speeds.

The LubriTose™ co-processed excipients have been developed to assist formulators with achieving more consistent performance and delivery characteristics, while meeting the industry challenges for faster, more consistent production. LubriTose combines a lubricant with a compression aid, allowing for the blending of the API, followed by tabletting, and does not require external lubrication at the end of the blending process. There are four grades of LubriTose™ products which are based on one of the following widely used compression aids, Anhydrous Lactose, Spray Dried Lactose, Microcrystalline Cellulose, and Mannitol, all of which are co-processed with Glyceryl Monostearate as the lubricant. 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 the API.

Testing substantiated that using LubriTose™ versus the traditional blend of an excipient and lubricant provides:

- Substantial benefit in flowability
- Similar lubricity properties without time sensitive overblending
- Improved content uniformity at high speeds

While we looked at model comparisons, API's can have a major impact on the type of product and how the product can be used. Our application experts will collaborate with you to develop a customized formulation for your specific needs.

Note: coating adhesion studies have been performed on LubriTose™ tablets and adhesion is not compromised.

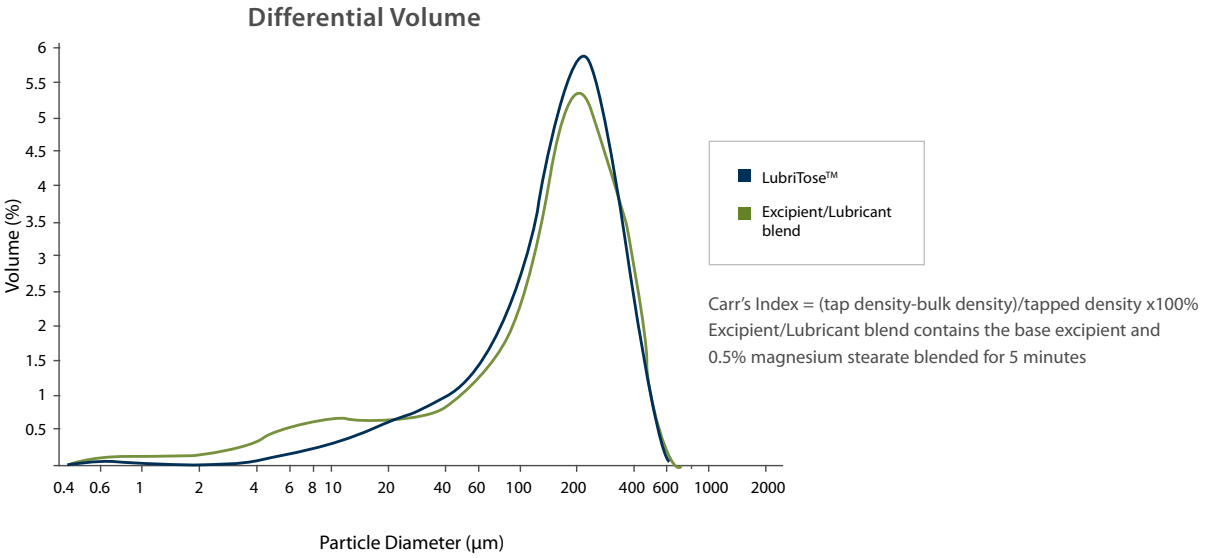
Improved Powder Flow

LubriTose™ has a lower angle of repose than the excipient/lubricant blend equating to better flowability. LubriTose™ products have a lower Carr's Index value than the excipient/lubricant blend. The values were less than 20, which ndicates good flowability.

PRODUCT	ANGLE OF REPOSE	CARR'S INDEX
LubriTose™ (lactose)	41	17.3
Lactose/Lubricant blend	45	22.2
LubriTose™ MCC	42	18.5
MCC/Lubricant blend	50	23.8
LubriTose™ (mannitol)	34	16
Mannitol/Lubricant blend	36	16.8

Better Flowability

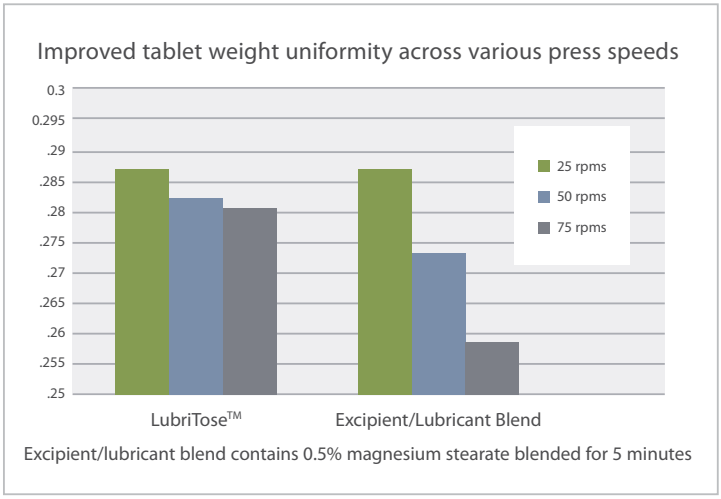
Lower amount of 'fines' (below 20 microns) equals less dusting and higher flowability



Carr's Index = (tap density-bulk density)/tapped density x100%
Excipient/Lubricant blend contains the base excipient and 0.5% magnesium stearate blended for 5 minutes

Tablet weight uniformity at increased press speed

Due to the improvement in flowability of LubriTose™ formulations compared to the excipient/lubricant blend, these formulations should be optimal for operating at high tablet press speeds. LubriTose™ was compared to an excipient/lubricant blend once again but at increasing press speeds. 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 below figure, LubriTose™, show minimal weight variation across various tablet speeds, which is indicative of a very uniform excipient blend that enables even and consistent flow. With the excipient/lubricant blend, 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.



- Optimal for operating at high tablet press speeds
- Minimal weight variation across various tablet speeds
- A very uniform excipient blend that enables even and consistent flow.

Improved Flowability for model API

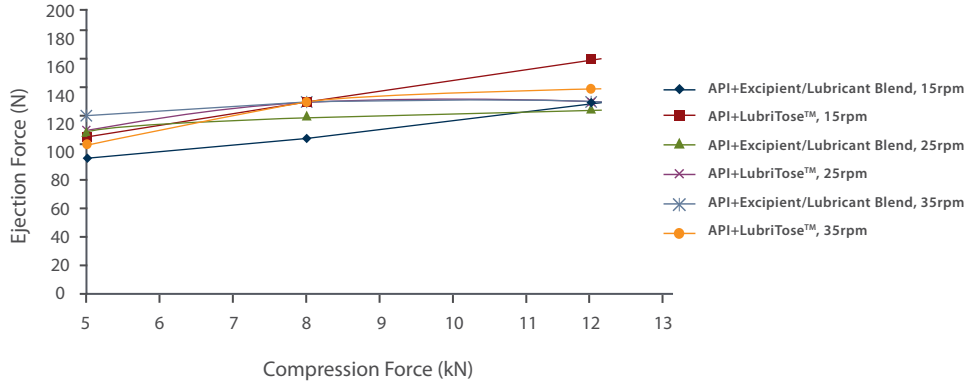
The flow properties of formulations using LubriTose™ were compared to excipient/lubricant blends. APIs were used in these formulas and blended with either LubriTose™ or a blend of compression aid and magnesium stearate. For all formulas tested, the flowability was better (Carr's index was lower) in the LubriTose™ versions. There was also a large improvement in the LubriTose™ MCC formulas compared to the excipient/lubricant blends.

		API PERCENTAGE	CARR'S
Ibuprofen	LubriTose™ (lactose)	80	15.9
	lactose/lubricant blend		22.9
	LubriTose™ (MCC)		27.0
	MCC/lubricant blend		36.3
Metformin hydrochloride	LubriTose™ MCC	40	22.2
	MCC/lubricant blend		40.8
Baicalein	LubriTose™ (lactose)	20	29.4
	lactose/lubricant blend		31.9
	LubriTose™ MCC		27.8
	MCC/lubricant blend		42.6
Aspirin	LubriTose™ (lactose)	50	20.9
	lactose/lubricant blend		23.4
	LubriTose™ MCC		25.1
	MCC/lubricant blend		40.2
Vitamin C	LubriTose™ (lactose)	40	23.0
	lactose/lubricant blend		25.8
	LubriTose™ MCC		24.1
	MCC/lubricant blend		43.4
Mefenamic Acid	LubriTose™ (lactose)	50	32.4
	lactose/lubricant blend		28.4
	LubriTose™ MCC		27.6
	MCC/lubricant blend		31.9
Piroxicam	LubriTose™ (lactose)	60	22.4
	lactose/lubricant blend		23.0
	LubriTose™ MCC		27.4
	MCC/lubricant blend		47.0

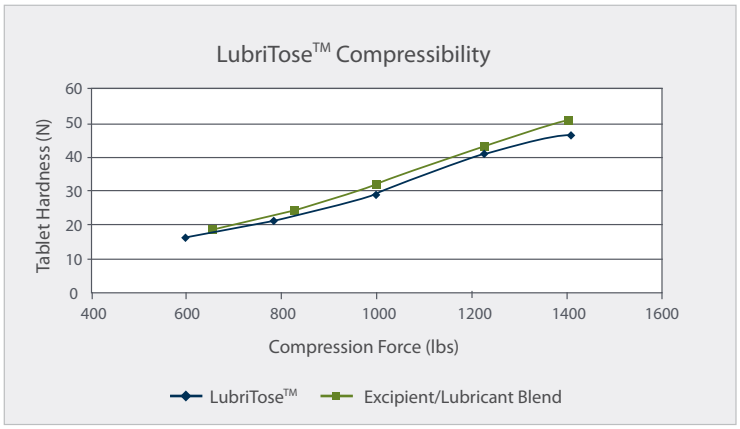
Notes: Carr's Index = (tap density-bulk density)/tapped density x 100%. Excipient/lubricant blend contains 0.5% Magnesium Stearate blended for 5 minutes.

No Effect in Lubricity & Compression

LubriTose™ demonstrates no effect on lubricity and compressibility. The ejection force of tablets made with LubriTose™ were compared to tablets made with an excipient/lubricant blend. The lubricity of LubriTose is equivalent to the formulas where Magnesium Stearate is used at all press speeds tested. Also as demonstrated, LubriTose™ will not lose compressibility and there is no reduction in tablet hardness.

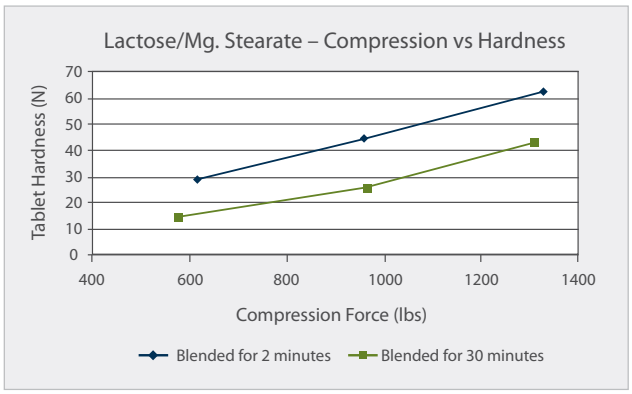


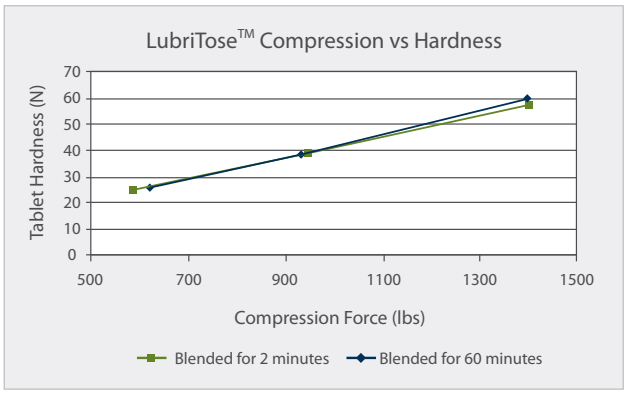
Notes: API (Ibuprofen) load was 60% of formula. Excipient/Lubricant blend contained 1.0% Magnesium Stearate and was blended for 5 minutes.



- Lubricity maintained
- No loss of compressibility
- Tablet hardness is not compromised

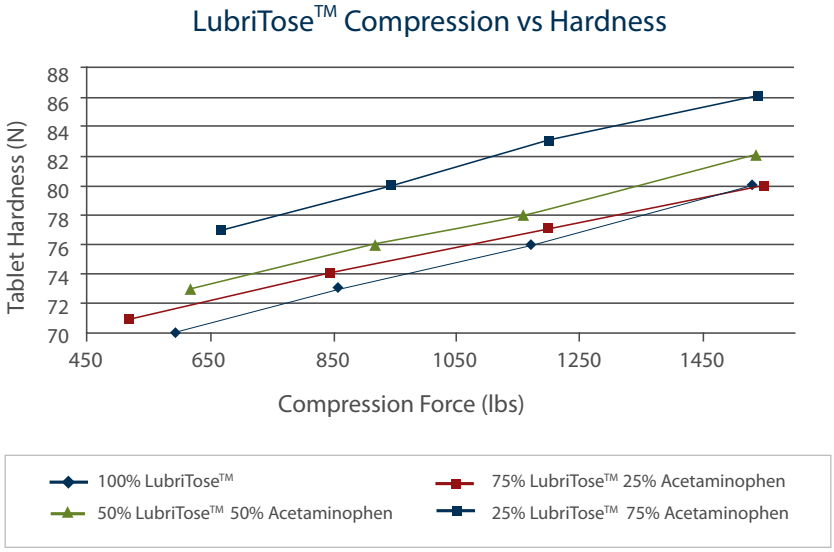
Notes: Excipient/Lubricant blend contains 0.5% magnesium stearate. Blending Time: 5 minutes





Minimal Usage Levels

LubriTose™ was tested by adding Acetaminophen to the product at increasing levels to observe ejection force and the point at which sticking or capping occurs. No sticking or capping was observed when using the recommended usage level of 25% LubriTose in the formula. Also, the ejection force decreased at increasing compression forces, meaning presses can be run at higher forces with less wear.



- Minimum recommended usage is approximately 25%
- Even at lower use levels, adequate lubrications is observed

No Impact on Dissolution with some APIs

The table below represents the dissolution of poorly soluble drugs with LubriTose™ compared to the excipient/lubricant blend. In the Lactose products, 5% Croscarmellose was added. Overall dissolution remained consistent when using LubriTose™. In some cases, a faster dissolution was observed. This may be due to the fact that since the disintegrant is added after the lubricant, it does not get coated over by the lubricant.

- Overall dissolution is not affected
- In some cases, a faster dissolution is observed

	DISSOLUTION (%)						
	Mefenamic acid	Piroxicam	Simvastatin	Ibuprofen	Baicalein	Puerarin	Breviscapine
LubriTose™ AN_a	75.2	100.4	103.7	90.9	62.7	96.5	80.2
Excipient/Lubricant blend	70.9	103.7	102.9	92.7	45.2	96.4	62.1
LubriTose™ MCC_b	Not done	89.4	102.2	90.5	67.0	54.3	66.5
Excipient/Lubricant blend	Not done	97.0	102.0	107.0	57.2	51.7	59.5

Notes: 'a' represents the addition of 5% of disintegrants; 'b' represents with no disintegrants. The excipient/lubricant blend contains 0.5% Magnesium Stearate blended for 5 minutes. Dissolution performed according to appropriate Pharmacopeia and recorded as % measured at listed monograph time.

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