Superior Lubrication Performance of Sodium Stearyl Fumarate (Alubra®)

in Direct Compression and Continuous Manufacturing

Meinolf Brackhagen[1], Mohammad S. Qadir[1,2], Heiko Feldmann[1], Christine Block[1]

[1] DuPont, Nutrition and Biosciences, Pharma Solutions, 29699 Walsrode, Germany

[2] DuPont, Nutrition and Biosciences, Pharma Solutions, Kings Court, Stevenage, Herts, SG1 2NG, UK.

INTRODUCTION:

Lubricants are agents added in small quantities to tablet and capsule formulations to improve certain processing characteristics such as decreasing friction, preventing adherence and improving flowability. For the last many decades, the process of lubrication is considered sensitive to overmixing leading to segregation, low hardness, increase in disintegration time and ultimately impacting tablet quality. Therefore, the most commonly used lubricant i.e. magnesium stearate (MgSt) is mixed with other ingredients just before tableting for minimum mixing time possible. This means there are at least a minimum of two steps required for tablet powder mixing. An alternative to MgSt is sodium stearyl fumarate (SSF, e.g. Alubra® from DuPont). It can provide enhanced dissolution, compatibility with range of APIs, flexibility in blending, improved compactibility with similar lubrication performance, and better tablet quality. Continuous manufacturing (CM) is currently a hot topic in the pharmaceutical industry[1]. In CM, the direct compression blending processes is conducted by two consecutive continuous dry powder blenders which separate the blending process into two distinct stages: the first blender is used for intensive mixing, whilst shear-sensitive materials such as the lubricant are introduced in the second blender. In order to provide more flexibility and reduce blending sensitivity associated with lubricants, this work investigates the effects of addition of SSF compared to MgSt in the first and second blending stages. In combination with colloidal silica, ~~a~~ lubricant effect on tablet hardness could be nearly suppressed or significantly reduced using SSF.

MATERIALS AND METHODS:

Tablets were composed of 500 mg Metformin, 196 mg MCC (Avicel® PH-102) or 200 mg co-processed MCC/SiO2 (containing 2% SiO_2, Avicel® SMCC 90), 14 mg croscarmellose (AcDiSol®) and variable contents of lubricant (MgSt or SSF (Alubra®)) and colloidal silica (Aerosil® 200). 2-step addition: The components (except the lubricant) were blended for 10 min., followed by addition of lubricant and further 3 min. blending. 1-step addition: As in the 2-step addition, except the lubricant was added from the beginning. Tablets were pressed on a manual single punch hydraulic press to produce 13 mm round, flat-facet tablets at a compaction pressure of 147 MPa. Tablet hardness and disintegration time were analyzed (n=3).

RESULTS AND DISCUSSION:

While a reduced lubricant effect on **tensile strength** was observed using SSF in 2-step and 1-step blending procedures with formulations containing PH-102 and no added SiO_2 (**Fig.1**), the effect was even more pronounced when co-processed SMCC was used (2% SiO_2 related to MCC, 0.56% related to the formulation, **Fig.2**).

Further addition of 1% SiO_2 to the PH-102 / SSF formulation nearly eliminated the lubricant effect on tablet hardness using the conventional 2-step blending (**Fig. 3**), while significant advantages where found at high lubricant levels (1-2%) in 1-step addition.

At higher SiO_2 content (2%), advantages in tablet hardness for lubricant SSF were found at higher lubricant levels, 1% and above for the 2-step procedure and 2% in case of the 1-step procedure (**Fig. 4**).

Disintegration times were generally between 10 and 30 seconds, increasing with lubricant level. Despite significant differences in tensile strength, dissolution times were comparable using either MgSt or SSF (e.g. **Fig. 5** compare **Fig. 1** for corresponding tensile strength). However, the co-processed SMCC appears to have a consistently lower disintegration time (**Fig. 6** – compare **Fig. 2** for corresponding tensile strength)

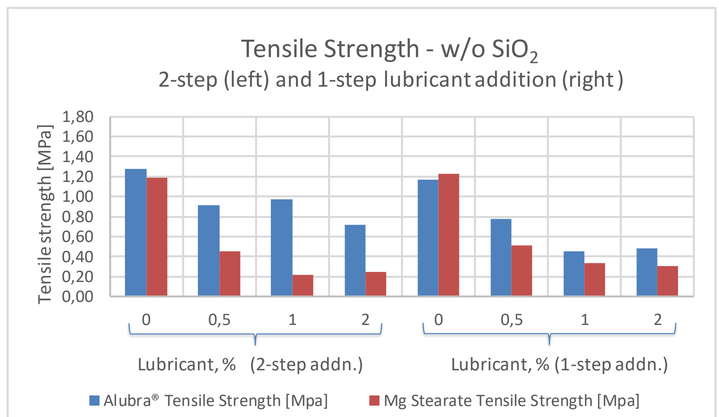

Fig. 1. Tensile strength of PH-102 tablets depending on lubricant addition

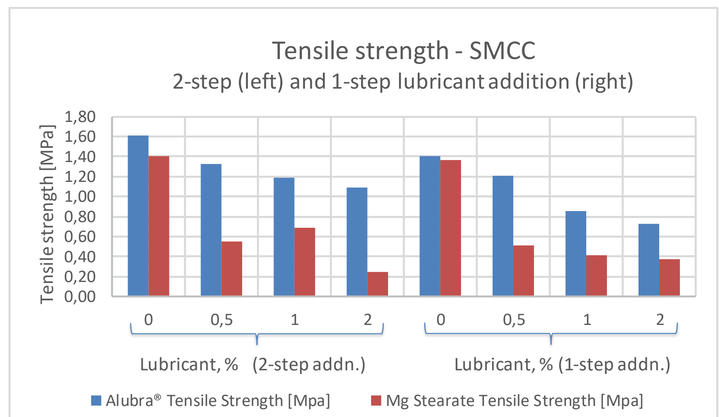

Fig. 2. Tensile strength of SMCC 90 tablets depending on lubricant addition

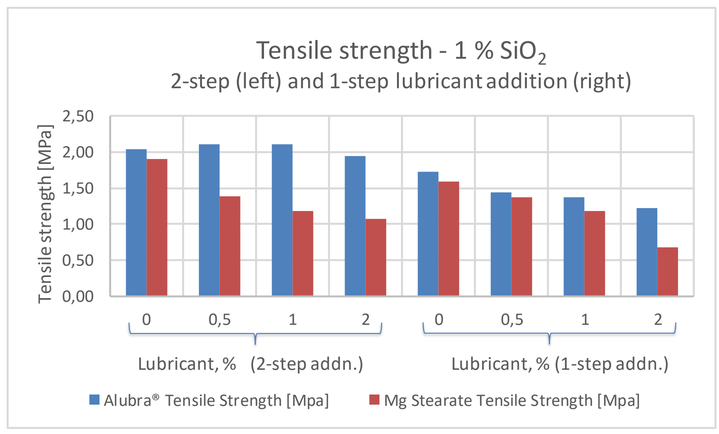

Fig. 3. Tensile strength of PH-102 tablets depending on lubricant addition with 1% SiO2 added

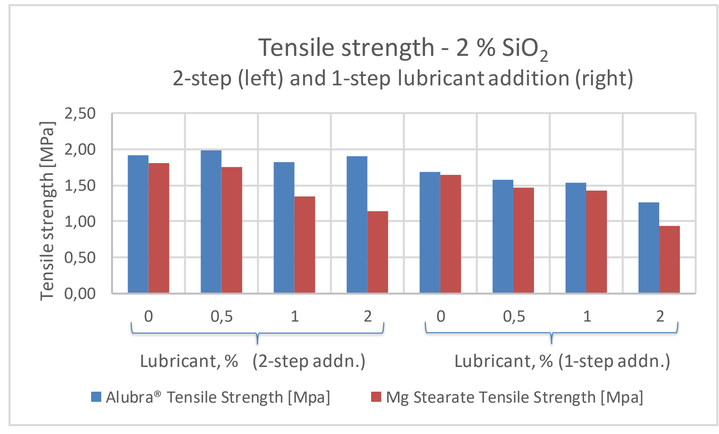

Fig. 4. Tensile strength of PH-102 tablets depending on lubricant addition with 2% SiO2 added

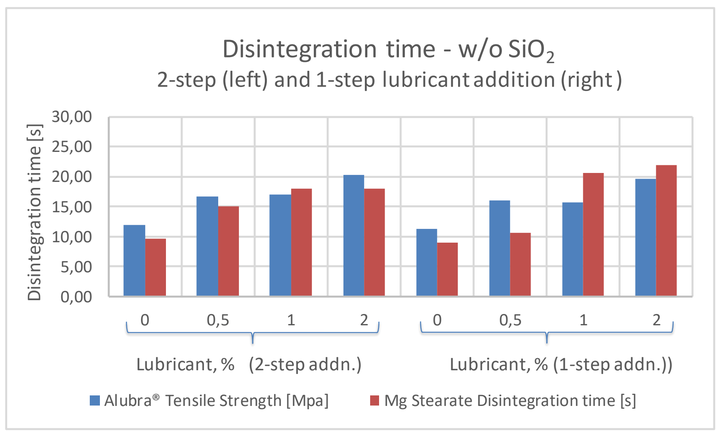

Fig. 5. Disintegration time of PH-102 tablets depending on lubricant addition

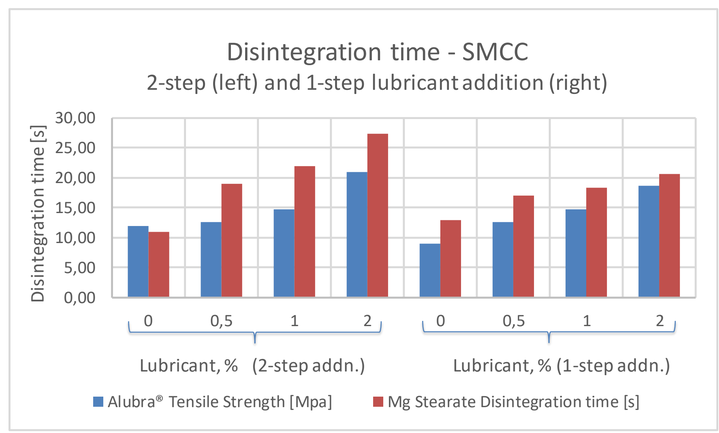

Fig. 6. Disintegration time of SMCC 90 tablets depending on lubricant addition

SUMMARY:

It has been demonstrated that SSF (Alubra®) can help to avoid over-lubrication especially at lower mixing time (2-step addition), nearly independently of the amount used and the presence of colloidal silica. In the case of prolonged mixing in the presence of the lubricant (1-step addition), the benefits of SSF (Alubra®) are seen predominantly in combination with co-processed SMCC or at lubricant addition levels ~2% in case of externally added SiO_2. Higher tensile strength using SSF did not compromise dissolution time, which was similar to or lower than in formulations using MgSt.

Nutrition & Biosciences
August-Wolff Str. 13
29699 Walsrode, Germany
Tel: +49 151 20966038
Meinolf.brackhagen@dupont.com
www.dupontnutritionandbiosciences.com

References: ***1***. Continuous Manufacturing of Pharmaceuticals, edited by Peter Kleinebudde, Johannes Khinast, Jukka Rantanen, John Wiley & Sons, 2017. ISBN:9781119001348,