# Excipient–Process Interactions and their Impact on Tablet Compaction and Film Coating

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**ABSTRACT:** The objective of this study was to establish the effects of the level of minor formulation components (sodium lauryl sulfate: SLS, and magnesium stearate: MgSt) and manufacturing process on final blend compaction properties and the performance of the tablets during film coating. A 2 × 2 × 3 factorial study was conducted at two levels of SLS (0% and 1%, w/w) and MgSt (0.5% and 1.75%, w/w), along with three different manufacturing processes (direct compression, high-shear wet granulation, and dry granulation). The tablets were compressed to the same solid fraction (0.9) and the resulting tablet hardness values were found to vary over a range of 13–42 SCU, highlighting large compactability differences among these batches. Increase in the level of SLS or MgSt in the formulation had a significant negative effect on compactability and the performance of film-coated tablets. The detrimental effects on compaction and coating performance were magnified for the dry granulation process, likely due to the overall increased shear experienced by excipients (SLS, MgSt, microcrystalline cellulose) during the roller compaction and milling steps. The findings of this study highlight the importance of the manufacturing process when considering the use-level of formulation components such as SLS and MgSt in the formulation. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:3666–3674, 2014

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## INTRODUCTION

Three types of manufacturing techniques are commonly used for formulating tablets—direct compression (DC), wet granulation (WG), and dry granulation (DG). Although DC is the simplest of the three, it may not always be feasible due to challenges with flow, compaction, and content uniformity.[1,2] Granulation can overcome most of these challenges and can be performed either in a wet or dry manner. WG is usually performed in a high-shear or fluid-bed granulator. The use of water during WG can sometimes lead to form change and/or chemical instability of the drug.[3,4] DG, using roller compaction, is commonly used given the ease of use, the fact that there is no drying step, and the continuous nature of the process.

When formulating APIs with low aqueous solubility, it is a common practice to add a surfactant such as sodium lauryl sulfate (SLS) to the formulation. SLS is an effective wetting agent and has been shown to offer significant dissolution enhancement of poorly water-soluble drugs.[5] However, SLS also exhibits lubricant properties, and, therefore, could potentially pose processing challenges depending upon its use-level. In a recent study by Aljaberi et al.[6] it was shown that a 0.57% (w/w) of SLS in a wet granulated formulation offered the desired dissolution profile without compromising the compaction properties of the granules. In another study by Moore et al.,[5] it was shown that the mode of incorporation of SLS during a DG process affected the compaction properties. It was concluded in that study that adding SLS during the final blending step, rather than before the granulation process, can prevent the loss in compaction without affecting the dissolution behavior significantly. Thus, for that particular formulation, an intimate contact between the API and SLS was not found to be necessary for dissolution performance. However, Aljaberi et al.[6] found in their experiments that an intimate contact between the API and SLS was critical in obtaining the desired dissolution profile. This demonstrates that this observation may be formulation-specific and/or that the granulation process (and sometimes even the test methods) played a role in the observation.

Even though SLS has some lubricant properties, it is not as effective a lubricant as stearates. Therefore, an additional lubricant may still be needed in formulations containing SLS. Commonly used lubricants such as magnesium stearate (MgSt) have a high surface area, low particle size, film or layer forming tendency, amphiphilic activity, and low shear stress.[7–9] MgSt has a very low maximum shear stress (85 kg/cm$^2$) and has little affinity for metal surfaces. MgSt has been shown to form a thin film on the surface of its carrier particle and is known to cause dissolution challenges due to the hydrophobic nature of the groups it presents on the surface.[10] Lubrication with MgSt causes a decrease in the compactability of the blend, but helps in mitigating punch sticking and reduces the ejection forces experienced by the tablets during compaction.

Several lubrication studies have been conducted showing the risks of over-lubrication related to MgSt.[7,11–13] These studies establish that the concentration of MgSt and blending factors such as blending time, blending speed, and blender scale can have an impact on granule compaction. It was also shown that MgSt can have a negative impact on the coating performance of tablets, with a higher number of logo bridging coating defects observed at higher MgSt concentrations. This was explained by the hydrophobic nature of MgSt that renders the tablet core

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**Table 1.** Experimental Design Details on the Split of SLS and MgSt Between the Intra- and Extragranular Portions for the Three Manufacturing Processes

| Batch # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Direct Compression | | | | Wet Granulation | | | | Dry Granulation | | | |
| Intragranular portion | | | | | | | | | | | | |
| MgSt | – | – | – | – | 0 | 0 | 0 | 0 | 0.25 | 0.25 | 0.75 | 0.75 |
| SLS | – | – | – | – | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 |
| Extragranular portion | | | | | | | | | | | | |
| SLS | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| MgSt | 0.5 | 0.5 | 1.75 | 1.75 | 0.5 | 0.5 | 1.75 | 1.75 | 0.25 | 0.25 | 1 | 1 |
| Total | | | | | | | | | | | | |
| SLS | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 |
| MgSt | 0.5 | 0.5 | 1.75 | 1.75 | 0.5 | 0.5 | 1.75 | 1.75 | 0.5 | 0.5 | 1.75 | 1.75 |

to be quite hydrophobic in nature, which in turn results in a loss of adhesion between the tablet substrate and the coating film.[14–18]

There are two important aspects in this field that have not been explored, and form the motivation for the current work: (1) interaction of the effects of SLS and MgSt with the manufacturing process, and (2) the impact of manufacturing process and SLS level on tablet coating performance. With this knowledge-gap in mind, the objective of this work is to establish the main effects and interactions of manufacturing process, SLS level, and MgSt level on the final blend compaction properties and performance of the core tablets during the film coating. A DOE (design of experiments) study was conducted using two levels of SLS (0% and 1%, w/w), two levels of MgSt (0.5% and 1.75%, w/w), and three different manufacturing processes (DC, WG, DG). The responses of the DOE study included granule compaction properties and performance of core tablets during film coating as measured by logo bridging coating defects.

## MATERIAL AND METHODS

The formulation used in this study consisted of approximately 1:1 ratio of anhydrous lactose and microcrystalline cellulose and 4% w/w croscarmellose sodium (distributed equally between intragranular and extragranular additions). The concentrations of SLS and MgSt were varied according to the study design using microcrystalline cellulose as the compensating excipient. Microcrystalline cellulose (Avicel® PH101) and croscarmellose sodium were purchased from FMC Corporation (Philadelphia, Pennsylvania). Anhydrous lactose (60M) was purchased from Kerry Bio-Sciences (Norwich, New Jersey), SLS from BASF (Dusseldorf, Germany), and MgSt from Mallinckrodt Chemicals (Saint Louis, Missouri). A HPMC-based Opadry® coating system (Colorcon, North Wales, PA) containing polyethylene glycol 400 (PEG 400) as a plasticizer was utilized for the coating studies. All excipients used in this study met the USP/NF requirements and the same lots of excipients were used throughout the study.

### Experimental Design

A 2 × 2 × 3 factorial DOE study was conducted at two levels of SLS (0% and 1%, w/w), two levels of MgSt (0.5% and 1.75%, w/w), and three different manufacturing processes (DC, WG, DG). The split of SLS and MgSt between the intragranular and extragranular portions (for the DG and WG batches) of these excipients are shown in Table 1 and explained in the subsequent manufacturing process section. Statistical regression analysis was conducted using JMP® statistical software (SAS).

### Manufacturing Process

The three manufacturing processes used in this study are described below (Fig. 1). The blending conditions such as, blender scale, blending time, and blender speed were maintained constant across all batches to eliminate any blending-related differences in blend lubrication. Final blends from each of the manufacturing processes were compressed into oval-shaped tablets at a press weight of 200-mg using embossed punches. These oval-shaped tablets were used for the coating performance evaluation. For film coating studies, the tablets were compressed to a solid fraction of 0.9. Compaction profiles (over a range of solid fractions) using flat-faced punches were generated using a Stylcam® compaction simulator (Medel'Pharm, Beynost, France) press to compare compaction properties across different batches.

#### *Direct Compression*

Direct compression batches were manufactured at a 4-kg batch size. SLS was added along with anhydrous lactose, microcrystalline cellulose, and croscarmellose sodium to a 25-L bin blender and blended at 25 rpm for 263 revolutions. MgSt (prescreened) was then added to the blender and blended for 100 revolutions at a speed of 25 rpm. A schematic diagram of the DC process is shown in Figure 1a.

#### *Wet Granulation*

Wet granulation experiments were conducted in a 30-L GEA Pharmaconnect® (Columbia, Maryland) high-shear granulator at a 6-kg batch size. SLS was added as part of the intragranular components. During preblending, liquid addition, and wet massing steps, the impeller tip speed was kept at 4.8 m/s, and the chopper speed was kept at 1500 rpm. Preblending was performed for 3 min. Water was used as the granulating fluid and was added to the granulator at a rate of 100 g per min per kg through a tube attached to a precalibrated pump. After water addition, the granules were wet-massed for 1 min. The wet granules were then passed through a Quadro® Comil Model 197S (Quadro Engineering, Waterloo, Ontario) running at 1300 rpm using a 8 mm opening screen and dried in a 25-L Freund Vector fluid bed at an inlet temperature of 50°C to a target LOD