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Tablet mechanics depend on nano and micro scale adhesion, lubrication and structure

Maria Badal Tejedor [a,b], Niklas Nordgren [a], Michael Schuleit [c], Mark W. Rutland [a,b], Anna Millqvist-Fureby [a,*]

[a] SP, Technical Research Institute of Sweden, Box 5607, SE-114 86 Stockholm, Sweden
[b] KTH Royal Institute of Technology, Division of Surface and Corrosion Science, Drottning Kristinas väg 51, SE-100 44 Stockholm, Sweden
[c] Novartis Pharma AG, Novartis Institutes for Biomedical Research, GDC, Novartis Campus, 4002 Basel, Switzerland

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ABSTRACT

Tablets are the most convenient form for drug administration. However, despite the ease of manufacturing problems such as powder adhesion occur during the production process. This study presents surface and structural characterization of tablets formulated with commonly used excipients (microcrystalline cellulose (MCC), lactose, mannitol, magnesium (Mg) stearate) pressed under different compaction conditions. Tablet surface analyses were performed with scanning electron microscopy (SEM), profilometry and atomic force microscopy (AFM). The mechanical properties of the tablets were evaluated with a tablet hardness test. Local adhesion detected by AFM decreased when Mg stearate was present in the formulation. Moreover, the tablet strength of plastically deformable excipients such as MCC was significantly decreased after addition of Mg stearate. Combined these facts indicate that Mg stearate affects the particle–particle bonding and thus elastic recovery. The MCC excipient also displayed the highest hardness which is characteristic for a highly cohesive material. This is discussed in the view of the relatively high adhesion found between MCC and a hydrophilic probe at the nanoscale using AFM. In contrast, the tablet strength of brittle materials like lactose and mannitol is unaffected by Mg stearate. Thus fracture occurs within the excipient particles and not at particle boundaries, creating new surfaces not previously exposed to Mg stearate. Such uncoated surfaces may well promote adhesive interactions with tools during manufacture.

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1. Introduction

Oral solid dosage is one of the most popular forms of drug delivery due to ease of handling and administration. The production process is furthermore relatively simple as are distribution and storage (Aleksovski et al., 2015; Kaur, 2012). A tablet is constituted of a wide range of particulate materials that are bound together under pressure to be delivered as a unit. Processing conditions as well as the physical and chemical nature of the particulate excipients and the active drug compound are both important for the binding of the blend and, consequently, the tablet properties (Hamad et al., 2010; Hoag, 2008b; Jain, 1999). However, the contribution of the excipients properties to the manufacturing process is not yet fully understood; especially, the role of the surface properties of the excipients and their contribution to the complex behavior of the formulation during tableting.

Several studies have been conducted to evaluate the compactibility and compressibility of different excipients. The approaches for evaluation are diverse since both powder properties and processing parameters can affect tableting and the resulting tablet properties. (Sinka et al., 2009; Sun, 2011; van Veen et al., 2000). The formation of bonding bridges between the single powder particles during tableting is an important factor that causes particle–particle adhesion contributing to the overall tablet cohesion. The formation of particle–particle bonds is driven by intermolecular forces and promoted by an enlargement of the contact area under pressure. These forces are mostly Van der Waals and hydrogen bonding interactions which become stronger at short range (Patel et al., 2006). Therefore the probability of bonding formation increases when the interparticulate distance is reduced. Other forces such as electrostatic interactions are also relevant to the particle–particle bond formation acting over a longer range. However the mechanisms by which the formation of bonding sites

* Corresponding author. Tel.: +46 768640046.
E-mail address: Anna.Fureby@sp.se (A. Millqvist-Fureby).

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is promoted depends on the behavior of the excipients under pressure. Plastic materials reduce their interparticle distance by irreversible deformation while brittle materials increase the area of contact through fracture and/or particle rearrangement. After the release of the compaction force a decrease of the contact area might occur if the materials exhibit an elastic component. The recovery of the deformation after removal of the compaction force will diminish the interparticle adhesion forces affecting the tablet strength and the overall tableting performance of the excipients (Amidon et al., 2009; Nyström et al., 1993). When surface interactions are evaluated between particles at the nanoscale, particle surface roughness influences the effective contact area between particles, thus affecting the overall magnitude of the intermolecular forces (Jallo et al., 2011). Additionally, processing parameters can modify the mechanical behavior of the excipients and particle surface interactions: the operating range of temperature and relative humidity can affect the powders depending on their viscoelastic and hygroscopic properties (Harding et al., 2008). However, a certain level of humidity is desired since water can act as a binder and as a plasticizer in the formulation (Doelker, 1993). Tableting parameters such as applied load and its duration are also adjusted and optimized as a function of the mechanical behavior and binding strength of the excipients in order to obtain consistent tablets (van Veen et al., 2000).

During powder tableting, the individual particles are not only in contact with each other but also with the surface of the tools. The physical interaction between the particles and the tool surfaces is influenced by friction and adhesion which arise from a possible combination of different intermolecular Van der Waals forces, electrostatic forces, electrical double layer formation and capillary forces (Saniocki, 2014). These phenomena also have an impact on the powder bulk microstructure during the tableting process and affect the tablet hardness. Consequently, the degree of adherence of the particles to the tools is strongly influenced by the level of adhesion and cohesion forces between and within the materials that comprise the powder blend. In some cases, a poor performance of the formulation can cause adhesion of the powders to the tools leading to imperfect tablet surfaces, commonly known as 'sticking'. Thus, in order to improve tableting performance avoiding particle-tool adhesion and friction forces, a small amount of lubricant (typically Mg stearate) is usually added to the formulation (Moody et al., 1981; Wang et al., 2010). During blending Mg stearate spreads over the surface of the particles forming at least a partial monolayer and filling the cavities on the surface of the particles (Roblot-Treupel and Puisieux, 1986). Despite the relatively thin coating, the effect on tablet properties can be significant.

Today, the performance of the excipients and active drug compounds during tableting can be predicted by the acquired knowledge of their mechanical and chemical properties together with tableting operation experience (Hamad et al., 2010; Toyoshima et al., 1988). However, this approach has not proved to be sufficient to solve all the problems arising during tableting (Matero et al., 2013). There is a lack of fundamental understanding regarding the particulate surface and interfacial properties in relation to the conformation of the tablet structure. A deeper study to better understand the interfacial processes occurring at the nanoscale level is needed, as well as their impact on the particle adhesion and material cohesion. Therefore, the development of analytical methods and new protocols to improve material characterization is essential.

The aim of this work is to study tablet surface properties in relation to the internal tablet structure and formulation using different tablet components and process parameters. The excipients selected for the present study are microcrystalline cellulose (MCC), lactose, mannitol and Mg stearate as a lubricant agent. They are all commonly used pharmaceutical excipients and they constitute a large percentage of the total weight of the tablet formulation, except Mg stearate, which is present in a very low amount. Comparative observations will be conducted since the excipients have shown different behaviors during tablet processing; lactose and mannitol are associated with tableting adhesion problems although mannitol has shown to be more problematic than lactose (Alderborn and Nyström, 1996). On the contrary, MCC is well-known as a non-sticky and easily compressible excipient (Alderborn and Nystrom, 1996; Doelker, 1993). In order to characterize and evaluate the tablets and the corresponding powders, a set of analytical tools has been used. Evaluation of tablet surface roughness and interfacial adhesion has been performed utilizing atomic force microscopy (AFM) a highly versatile tool employed by some of the authors over the last decade for studying a wide range of interfacial and contact phenomena at the nanoscale (Feiler et al., 2005, 2007; Mizuno et al., 2010; Nordgren and Rutland, 2009; Ralston et al., 2005; Rathje et al., 2014; Wang et al., 2003). Other complementary techniques, i.e., scanning electron microscopy (SEM) and profilometry have been used for macroscopic surface roughness and tablet morphology evaluation. As to link the surface properties of the tablet with their structural properties, a tablet hardness test was used to establish the tablet binding strength.

2. Experimental

2.1. Materials

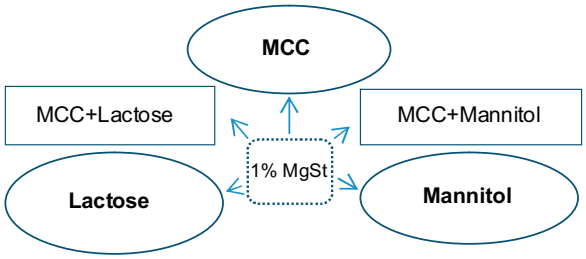
The materials used in this study are common pharmaceutical excipients: microcrystalline cellulose (Cellulose Microcr. PH200, FMC), lactose (Lactose spray dried, Meggle), mannitol (Mannitol 200SD, Merck) and magnesium stearate (Magnesium stearate Pharma, FACI); the excipients were provided in powder form.

2.2. Preparation of tablets

One-, two- and three-component formulations were prepared (Table 1). Single component formulations consisted of pure excipients (MCC, lactose or mannitol). Two component formulations consisted of MCC blended with either lactose or mannitol in a 1:1 mass ratio. Mg stearate was used as a lubricant in a proportion of 1% of the total weight of the blend. Both single components and two components formulations were lubricated with Mg stearate obtaining a three component formulation.

When the tablet formulation consisted of more than one excipient, the mixing of the blend was performed with a vortex mixer which provided a homogeneous and mechanical mixing of

Table 1
Schematic figure depicting the different tablet formulations used; one, two and three component systems. The composition of the formulations consisting of two components (in boxes) was equal to 1:1 mass ratio. The case where a total amount of 1% of MgSt was added to the pure excipient and two component formulations was also studied.



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