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Towards a better understanding of dry binder functionality

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ABSTRACT

It is of great importance to get a deeper understanding of the binding behaviour and functionality of different types of dry binders, since dry binders are crucial to ensure appropriate properties of dry granules and tablets. Based on previous studies, the most effective dry binders of chemically different types have been chosen to apply a new approach analysing the compressibility of tablets made from pure dry binders. Therefore, tablets were compressed at different tableting speeds to reveal binding behaviour of dry binders. Viscoelasticity, plasticity or abrasiveness were derived from force-displacement curves of tablets, which were manufactured at varying tableting pressure. In addition, elastic recovery, tabletability, fracture energy and out-of-die Heckel analysis were performed in order to get a comprehensive understanding on mechanical properties of dry binder for tableting. The new approach indicated explanations for results of previous studies in terms of tablet tensile strength, friability and dry granule properties. It enables a rational selection of dry binders for certain processes.

1. Introduction

1.1. Dry binder

Dry binders are important in direct compression to generate tablets with high tensile strength and low friability. They are also crucial in compaction/dry granulation (RCDG) to produce dry granules of sufficient size and a low fraction of fines (Jaminet and Hess, 1966; Kleinebudde, 2004). As a partial loss in tabletability after RCDG can occur, dry binders are desirable for RCDG to compensate loss in tabletability. Malkowska and Khan first addressed the partial loss in tabletability, as they observed a lower tensile strength after RCDG in comparison to direct compression (Malkowska and Khan, 1983). They described loss in tabletability by work-hardening of materials. However, no further evidence was found. Other studies exhibited that size enlargement and hardening of granules could cause a loss in tabletability (Herting and Kleinebudde, 2008; Sun and Himmelspach, 2006).

Different aspects, which will get potentially greater importance in the future, desired a better understanding on processes and raw materials. Continuous manufacturing could be beneficial to the pharmaceutical industry (Schaber et al., 2011). However, it is a great challenge implementing process analytical technology (PAT) tools and to get better understanding of processes and materials. In this context, it is crucial to gain a deeper understanding on mechanical and particle properties of APIs and excipients in order to determine feasibilities for continuous manufacturing processes (FDA, 2004). The functionality of excipients depends not only on the chemical composition, but also on their physical structure. A manufacturing classification system (MCS) regarding API properties was proposed in order to evaluate, which manufacturing route is reasonable to get desired tablet properties on the one hand and save costs on the other hand (Leane et al., 2015). As MCS is based on properties of raw materials, it is of great importance to have a comprehensive understanding of raw materials. Beside APIs, a better understanding of the functionality of excipients is highly demanded.

Predominantly, plastically deformable and polymeric materials are used as dry binders (Kleinebudde, 2004). However, since some morphologies of brittle materials generated high tensile strengths of tablets in recent studies, brittle and inorganic materials could also be considered as dry binders (Grote and Kleinebudde, 2018; Hagelstein et al., 2018). In order to assess the effectivity and efficiency of dry binders for direct compression or RCDG, different studies have been investigated. Several studies addressed connections between MCC properties and tabletability (Landín et al., 1993; Shlieout et al., 2002), while the most important parameter of MCC seems to be the particle size (Herting and Kleinebudde, 2007). Using always one type of HPC, methyl cellulose (MC), starch and povidone (PVP) in formulations in a fraction of 6%, HPC resulted in the lowest friability and ejection force in direct compression, while starch was unsuitable as dry binder (Joneja et al., 1999). Moroni tested one quality of copovidone in comparison to a hydroxypropylmethyl cellulose (HPMC) and a microcrystalline cellulose (MCC) in different fractions in terms of crushing strength,

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dissolution, ejection force and crushing strength after RCDG (Moroni, 2001). Herting et al. compared seven different dry binders for RCDG and subsequent tableting in terms of granule size and tabletability. In this study, ribbons with a defined porosity were produced in contrast to other studies at which constant specific compaction forces were applied (Herting et al., 2007). They introduced a new type of fine-particle copovidone (Kollidon VA64 Fine, BASF, Germany), which was most suitable beside a micronized grade of crospovidone (Kollidon CL-M, BASF, Germany). A fine-particle hydroxypropyl cellulose (HPC-SSL-SFP, Nisso, Japan) was first introduced by Skinner et al. (Skinner et al., 1999) and later compared to seven other dry binders by Mangal et al., by including the best binders of previous studies. Fine-particle hydroxypropyl cellulose (HPC) was most effective regarding granule size and tensile strength of resulting tablets in a fraction of 10% followed by the fine grade of copovidone. They further described a dependency of dry binder particle size on the effectiveness for granule size enlargement and tensile strength of tablets (Mangal et al., 2016). Other authors tried to explain the tabletability of HPMC- or chitosan-qualities via different molecular weights or glass transition temperatures (Alakayleh et al., 2016; Khatri et al., 2018; Nokhodchi et al., 1996), while the particle size was ignored or only subordinately addressed.

In a previous study, we performed a comprehensive comparison of 18 different dry binders at 10% fraction in a formulation with mainly paracetamol and dibasic dicalcium phosphate in terms of granule properties, tensile strength, friability and disintegration time (Arndt and Kleinebudde, 2018a). We found that within a chemical type of binder, the granule size, fraction of fines, friability, tensile strength and disintegration time could be correlated to the mean particle size of the binders. Since no correlation was found to describe differences between types of binders, additional factors are required to understand functionalities of different types of binders. Therefore, dry binders' mechanical properties were investigated in this study for the first time to gain a deeper understanding of dry binder functionality. Based on the described studies, the most effective dry binders of five different chemical types have been chosen for this study.

1.2. Mechanical analysis

A variety of compaction data analysis methods are known to access the behaviour of excipients during compaction (Çelik, 1992). Often used in the pharmaceutical field are the compression analyses according to Kawakita (Kawakita and Lüdde, 1971) or Heckel (Heckel, 1961). The compression analysis according to Kawakita is based on the volume of the material during tableting in relation to the initial powder volume of the material and the compression analysis according to Heckel based on the solid fraction during tableting in relation to the particle density. Out of several compression analyses, it is possible to calculate characteristic compression parameters, which are descriptors of plasticity (Klevan et al., 2009; Klevan et al., 2010; Leuenberger, 1982). The yield pressure from Heckel analysis was criticized, as it reflected often not the entire compressibility curve and is strongly depended on the true density measurement (Sonnergaard, 1999; Sun, 2008). Nevertheless, yield pressure and indentation hardness was more distinctly correlated in comparison to the plasticity parameter of the Kawakita plot, but less distinct in comparison to the plasticity parameter of the Kuentz and Leuenberger equation (Kuentz and Leuenberger, 1999; Paul and Sun, 2017). In general, in-die compression analysis led to results that might be not relevant for practical applications, since it includes elastic deformation and it disregards elastic relaxation (Sonnergaard, 1999; Sun and Grant, 2001). Typical model materials with different hardness and deformation behaviours were often compared for evaluations of compression analysis (Katz et al., 2013; Klevan et al., 2010; Paul and Sun, 2017; Persson and Alderborn, 2018; Roberts and Rowe, 1987), while in this study, various plastically deformable polymeric materials were compared to obtain differences in deformation behaviour. In this study, a novel approach was applied by investigating the crushing behaviour of tablets made from raw materials in contrast to conventional compression analyses, which are based on the compression of materials to compacts. In the pharmaceutical industry, tablets are analysed regarding crushing strength at one deformation speed. Different deformation speeds for tablets that were manufactured at different tableting pressures were investigated in this study to reveal viscoelasticity, plasticity and binding behaviour of dry binders. The new approach was complemented with established methods and parameters e.g. fracture energy, elastic recovery of tablets, tensile strength and out-of-die solid fraction analysis by interpreting the whole curve in order to get a comprehensive understanding of dry binder mechanical properties.

Table 1
Dry binders.

Product name	Chemical type of binders	Abbreviation	Supplier
Vivapur 105	Microcrystalline cellulose	MCC	JRS Pharma, Germany
HPC-SSL-SFP	Hydroxypropyl cellulose	HPC	Nippon Soda, Japan
Kollidon 12 PF	Povidone	PVP	BASF SE, Germany
Kollidon VA64 Fine	Copovidone	COP	
Kollidon Cl-M	Crospovidone	XPVP	

2. Materials and methods

2.1. Materials

Based on a previous screening of dry binders (Arndt and Kleinebudde, 2018a), the most effective binder of each chemical type of binders was chosen. Table 1 gives an overview of the dry binders that were used in this study.

2.2. Methods

2.2.1. Tableting

Before tableting, dry binders were stored for at least one week under climate conditions (45% RH, 21 °C). The production of tablets was performed by using a tablet simulator (Styl'One Evolution, Medelpharm, France) without pre-compression at a medium average tableting speed of approximately 14 mm/s and a real dwell time of 11 ms ± 3 ms, which is defined as the time span, at which 90% or more of the maximum pressure has been applied. Pure binders were compressed to 8 mm flat-faced tablets with a set mass of 130 mg without a glidant. The die was filled manually due to the low bulk density of the dry binders. Tableting experiments were performed under climate conditions (45% RH, 21 °C). Tablets were stored at least for one week under the same conditions before they were further characterised.

2.2.2. Characterisations of the dry binders

2.2.2.1. Resistance towards deformation test for tablets. Force-displacement curves of 8 mm flat-faced tablets ($n \geq 8$) made from pure binders (Section 2.2.1) were recorded by utilising a tablet simulator (Styl'One Evolution, Medelpharm, France) as universal testing machine. Therefore, each tablet was placed on the cross side in the middle of a flat faced lower punch with a diameter of 11.28 mm (Fig. 1). The lower punch was moving down to a depth of 10 mm and fixed at this position, so that the compression was only executed by the upper punch. The upper punch was moving down with a average speed of 0.01 mm/s ± 0.004 mm/s, 0.35 mm/s ± 0.05 mm/s, or 100 mm/s ± 30 mm/s to a distance of 4 mm between lower and upper punch. The medium test speed of 0.35 mm/s was chosen in order to mimic the standard test speed of a tablet tester (Smart Test 50, Sotax AG,