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Quality by design (QbD) approaches for the compression step of tableting

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Introduction: Although tableting is one of the most commonly used processes in drug manufacturing, the tablet formation process is still not fully understood, nor can it be fully controlled.
Areas covered: In this paper, recent approaches to correlate tablet mechanical properties with process parameters are discussed, covering (mainly) the last 5 years. These approaches are the basis for a future of rational formulation strategies, which may lead to optimum tablet properties within a shorter timescale, in contrast to the present empirical approach. The reader will on one hand gain an insight into current parameterization of the tableting process and evaluation strategies and on the other hand will gain an impression of the difficulties connected to the interpretation of a physically complex process and its impact on predictive modeling.
Expert opinion: The main consolidated findings are that even when using multivariate statistical approaches, it cannot be expected to find a global evaluation method that fully explains the mechanism of tableting, but that careful sequential evaluation is required. For further improvement, there is a need to use more complex models and alternative technologies, in order to increase both tablet quality and productivity.

Keywords: direct compression, mechanical properties, modeling, multivariate analysis, parameterization, particle properties, prediction, tablet

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1. Introduction

Today there are strong incentives for an increased understanding of material properties and pharmaceutical manufacturing processes: in-line monitoring and analysis of pharmaceutical processes are aimed at better process control and control of end-product quality. The main facilitator in this development has been the process analytical technology (PAT) initiative of the American Food and Dug Administration [1,2]. The purpose of the PAT guidelines is to increase the understanding and control of manufacturing processes in order to meet increased quality demands in terms of cost, efficacy, safety and product reliability. The objective is to assure and build in quality throughout the manufacturing process, also referred to as quality by design (QbD), and enable fast problem solving, if necessary [3]. Both design of experiment (DoE) and multivariate data analysis play a key role in the PAT initiative [4].

Holistic QbD approaches begin with a predefined target product profile and apply various principles and tools at different stages to better understand the product and the processes to ensure that the product consistently achieves the predetermined quality characteristics [5-7]. There has been a fundamental change in pharmaceutical manufacturing from manual to automated systems enabled by recent development in information technology. Application of integrated sensors and computer systems allow collecting data in real time. The processes can be assessed based on these

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data, and mathematical modeling enables prediction of certain quality attributes. The goal is to understand processes well enough to i) develop a mathematical model (usually polynomial) relating the critical process parameter (CPP) to critical quality attributes (CQA), ii) collect data throughout the process and iii) feed the data into intelligent computer systems that monitor the CPP and CQA in real time. Data collected in CQA at low and high values of CPP during research or process improvement is used to create multivariate mathematical equations or models, which describe the product and/or the processes. Development of a product in this way, with a range of equipment settings along with raw and in-process material variances, allows better control of both the product and the process. The multivariate mathematical coverage by this approach defines the design space [8,9].

Several pharmaceutical processes, such as granulation and film coating, have successfully been subjected to PAT applications by real-time monitoring of the process [4]. In-line instrumentation allows *in situ* analysis. Using noninvasive spectroscopic methods such as near infrared (NIR) or Raman, the probe does not even need physical contact with the product and problems related to sampling are avoided. Combination of PAT instrumentation and multivariate analysis provides tools for the effective process monitoring and control enabling detection of multivariate relationships between different variables such as raw materials, process conditions and end products [3,4].

In contrast to these processes, tablet manufacturing has not yet come so far with respect to QbD and PAT. In the following, we shall restrict the discussion to tablet manufacturing by direct compression, that is, the compression of dry powder blends/mixtures that comprise drugs and various excipients, which involves only few processing steps and excludes all the variables connected to granulation. The simplicity and cost-effectiveness of the direct compression process have positioned it as a preferred alternative over granulation. However, in the same way as any granulation-based processes, direct compression is highly influenced by the powder characteristics of the blend, such as flowability, compressibility and dilution potential (drug uptake capacity). Most formulations contain high amounts of excipients in addition to the drug, and consequently, these excipients play a major role in the functionality and processability of the formulation.

In order to manufacture tablets with consistent quality attributes, it is necessary to identify a process control tool that, first, correlates critical material attributes of dry powder blends with their tableting properties and, second, can be controlled in real time to ensure that the variation is within the limits of the respective material attribute. However, compared with other pharmaceutical production processes, compression is very fast (the actual compression event takes milliseconds only). It is a complex process, and the scale-up of a formulation will be a problem without a mechanistic understanding of material properties [10]. The current review aims at highlighting opportunities and challenges moving toward QbD in the context of the tablet compression step.

2. Basic characteristics of (single) materials for direct compression

The key to a successful, robust formulation and process is to understand the chemical and physical nature of the ingredients alone, and how their properties interact [11].

As to the concepts of QbD and PAT [1-10], in the case of tableting, there is a demand on the characterization of the materials (excipients) in terms of critical properties and steps of the tableting process and to the performance of the tablet in a risk analysis-based approach. These approaches have found their consequence in the regulatory guidelines for drug products in general, for example, in ICH Q8 Pharmaceutical Development [5]: any marketing authorization application should address the impact of excipients chosen on manufacturability and product performance, quality specifications and information about suppliers. 'Functionality-related characteristics of excipients' was, therefore, introduced to European Pharmacopoeia 6 (Ph. Eur. 6) [12] as a non-mandatory section. The section provides guidance referring to the functions of the substances when used as excipients. In addition to tests with given minimum requirements such as identity, chemical purity, microbial contamination and so on, functionality-related characteristics include those parameters that have been recognized as being relevant for the performance of the materials both in the manufacturing process and in the product properties.

The monograph states common functions of the respective substance used as an excipient and relevant characteristics together with suggested methods of measuring these; however, this information is not elaborate. It may rather be understood as a list of important descriptors of the quality of the material. It is up to the user to set the specifications according to their development validation, with a view to alternative suppliers and batch-to-batch variations as well. As an example, microcrystalline cellulose is – after Ph. Eur. 7 and United States Pharmacopeia (USP) 32 – basically used in tableting as a binder, diluent or disintegrant. For each of these functions, particle size distribution and powder flow are named as important features [13]. Another example, alpha lactose monohydrate, is used as a filler or diluent in solid dosage forms, for which particle size distribution, bulk and tapped density, including Hausner Index, are important [14]. Examples of functionality-related powder properties of excipients and suggested measuring methods covered by Ph. Eur. 7 and USP 32 are listed in **Table 1**.

In addition to the powder characterization methods named above, noninvasive spectroscopic methods, such as NIR and Raman, have proven to be useful tools to study consistency of raw materials [4]. Multivariate models reflecting the acceptable variation in basic powder properties of raw materials for a product can contribute to ensure a robust process, which in the scope of the present review, are the tableting step and tablet mechanical properties.

Table 1. Examples of relevant powder properties of excipients for the characterization of DC materials and suggested measuring methods according to pharmacopoeias (Ph. Eur. 7 and USP 32).

Functionality-related characteristics	Method for measuring	Alternative method(s)
Polymorphism/pseudopolymorphism	X-ray (single crystal) X-ray (powder)	Thermal analysis, IR, Raman, solid-state NMR
Degree of crystallinity	X-ray (powder)	Thermal analysis
True density	X-ray (crystal density; unit cell density)	
Particle density (pycnometric density)	Gas pycnometric density	Hg-porosimetry (intrusion)
Bulk and tapped density	Measuring cylinder and tapping mechanism	Volumeter
Particle size	Microscopy	Fractionation by sieving (cumulative)
Particle size distribution	Analytical sieving	Laser light diffraction
Specific surface area	Gas adsorption (dynamic gas flow method)	Gas adsorption (volumetric method)
Powder flow	Flow through orifice	Angle of repose; Hausner Index (compressibility); shear cells
Wettability	Sessile drop method (static contact angle)	Water uptake (Washburn method)
Viscosity (polymer solutions)	Capillary viscometer	Rheometer

IR: Infrared; NMR: Nuclear magnetic resonance; Ph. Eur. 7: European Pharmacopoeia 7; USP 32: United States Pharmacopeia 32.

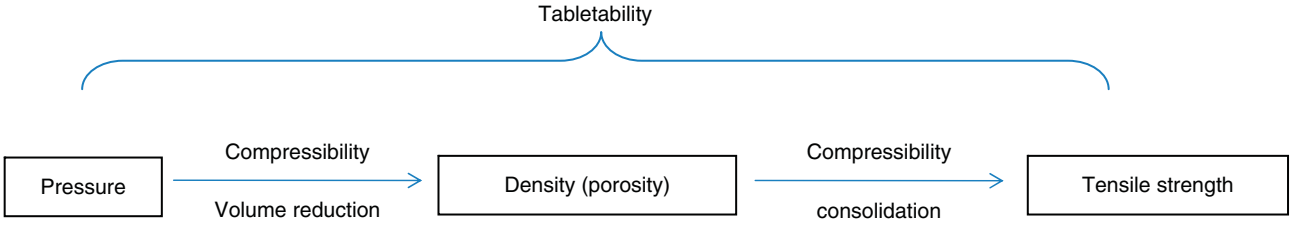

Figure 1. Definitions around the compression of tablets including the term tabletability, compressibility and compactibility (e.g., [15,16]).

3. Compression

Definitions around the compression of tablets include the general term tabletability, comprising compressibility and compactibility (**Figure 1**).

Tabletability is the ability to form tablets of certain properties under the pressure. It is often expressed as the tensile strength of the tablets as a function of the tableting pressure. It is important to remember that porosity is the most essential parameter for comparison of different materials! As a consequence, in order to follow the tablet formation in more detail, volume reduction versus time (compressibility) needs to be quantified.

3.1 Instrumentation/Sensors

For a quantitative description of the tableting event, accurate time-resolved force and displacement data are necessary. The significance of data inaccuracy on parameterization has been frequently discussed with respect to the reproducibility (intra-laboratory precision) and repeatability (inter-laboratory precision) [17].

Even compaction simulators particularly designed for data acquisition are no guarantee for good data [18-20]. For scientific purposes with certain requirements on accuracy and precision, it still seems advantageous to tailor-make the instrumentation and to validate it with special care.

3.2 A brief summary on the mechanism of compaction and tablet formation

Under the pressure, as a first step after overcoming friction and attraction forces, the particles are displaced and packed more densely. At spots of very high pressure, where two edges of two particles meet, the particles themselves will deform – elastically (depending on the material properties, this effect may be neglectable) – through plastic cold flow or

brittle fracture [21,22]. These types of deformation take place simultaneously at different spots in the compact, because neither the material typically is isotropic nor is the pressure distribution homogeneous [23-25]. In addition, plastic flow is time dependent and thereby the mechanical properties of the tablets depend on both the tablet machine construction (compression profile) and chosen tableting speed. Deformation mechanisms depend also on other material characteristics, for example, particle sizes. In general, the smaller the particles, the more pressure is needed for densification [22,26]. For composite particles, it depends on the particle structure (intra-particle porosity, degree of agglomeration, particle failure strength), in which deformation mechanism is predominant [27]. Any deformation leads to closer contact and to new contact surfaces between the particles, leading to increased adsorption bonds. The strengths of the adsorption bonds depend on the surface energy of the particles, rather than on the microstructure of the compact [28]: lower surface energy – within normal tablet porosity ranges – leads to decreased strength of the adsorption bonds. With further compression, the specific interparticle contact area increases. For tablets where the development of solid bridges is the main bonding mechanism, the particle surface energy is widely unimportant [27,28]. It should be mentioned that at higher pressures, further deformation may become more difficult due to strain hardening [29,30]. Furthermore, the densification takes place in confined space, which means that below a certain porosity, elastic deformation becomes predominant. The extent of the respective types of deformation determines the overall mechanical strength of the tablet; the processes are schematically depicted in **Figure 2**.

Table 2 summarizes some of the factors that in general determine the mechanical strength (tensile strength) of tablets with respect to types of bonds and deformation.

3.3 An example to illustrate the complex relationship between consecutive compaction steps and tensile strength

It is interesting to divide the tableting event into consecutive compaction steps by looking at dry granulation (by slugging or roller compaction) and subsequent tableting. The most common opinion is that dry granulation would compromise tabletability of the materials expressed in terms of tensile strength of the tablets [31,32], because a fraction of the particles' deformation abilities is already used for the densification to granules during the dry granulation step. The latter work [32] even develops a mathematical model for the effect of roller compaction on tableting properties of different blend ratios of lactose and microcrystalline cellulose: the two steps consecutively put together are combined to the tableting curve. In other words, the tableting event of granules produced by roller compaction starts at a later point of the pressure/strength curve compared with the non-processed material, and the increase in tensile strength with pressure is limited.

However, for certain materials, it has recently been observed that roller compaction and dry granulation do not *decrease* the strength of the tablets as expected from the above said, but, on the contrary, even increase their tensile strengths [33]. The explanation of this phenomenon on the supramolecular level is still to be found; amorphization as one possible mechanism is frequently discussed. Further parameters to consider are particle size changes, porosity of the granules, work hardening and surface effects due to lubrication. Therefore, the dependence between material behavior during compression and mechanical strength of the tablets remains complex [34].

4. Parameterization of tablet formation

The most used instrumentation, for controlling tablet production both in an industrial setting and in R&D, is to measure force (pressure) for each single tablet. **Table 3** gives an overview over selected, most commonly used parameterization methods to evaluate the compression event exclusively based on time-resolved force (pressure) data. Further development has introduced sufficiently accurate online displacement measurement, which made parameterization based on force and displacement measurement possible. The function between increased pressure and volume reduction is nonlinear and becomes disproportionately high with decreasing porosity. However, due to the different mechanisms of volume reduction involved under the constrained conditions, no simple (exponential) functions describing the entire pressure range are found, nor expected. This fact has led to numerous equations in order to cover as much of the pressure/volume curves as possible, a selection of which is also included in **Table 3**.

Recent research shows that in order to extract appropriate information using several compression functions on the same data, sequential handling of the parameters is useful. It should follow the logical order of events taking place during compression of the powder bed [35-37]: After die-filling, packing of the powder takes place; this has elements of particle rearrangement and fragmentation. Therefore, estimation of the particle rearrangement incidence should be carried out first, followed by investigations into fragmentation propensity. For estimation of particle rearrangement, the *ab* index from the Kawakita parameters a and $1/b$ has been suggested. The next step is a subcategorization of powder fragmentation propensities, using, for example, the Shapiro f parameter. Finally, the permanent deformation of the particles at higher pressures and higher densities (Heckel yield pressure) should be investigated independently of particle rearrangement and particle fragmentation, in the linear region of the Heckel plot. The outlined sequential handling of data ensures that the material properties are classified in their order of importance, thus reducing the risk of misinterpretation. In other words, classification according to particle deformation, employing yield pressure, is not recommended without first knowing the extent of particle rearrangement and fragmentation. It has been known for a long time that particle

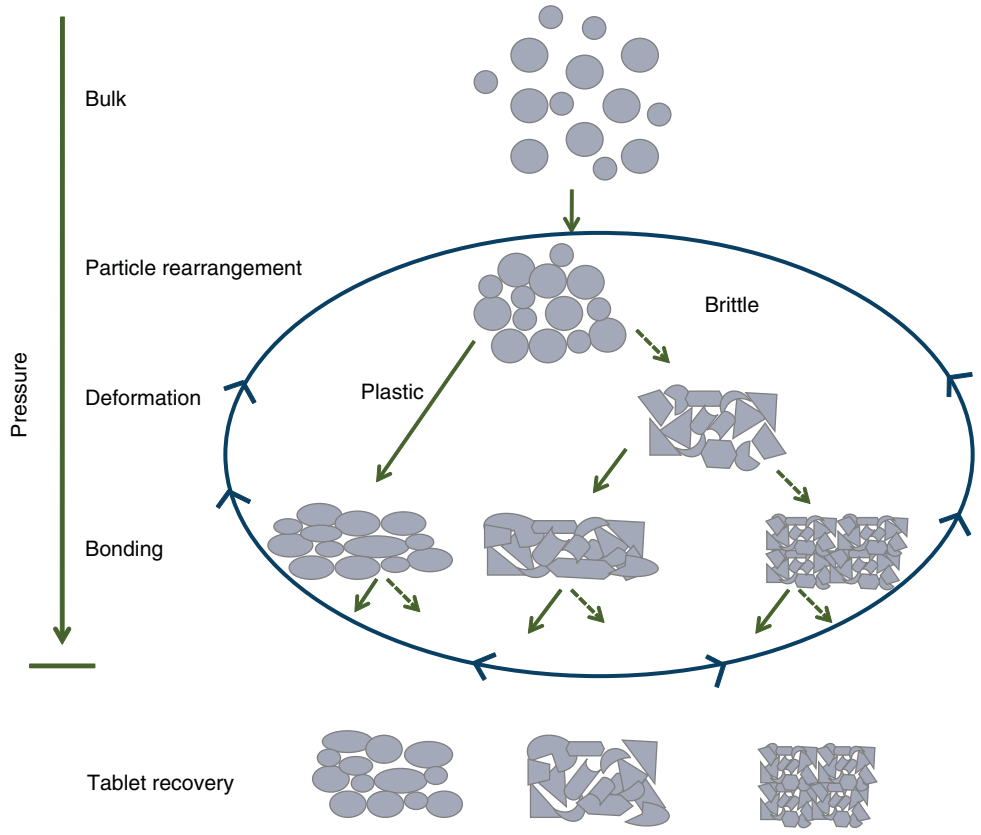

Figure 2. A schematic depiction of processes contributing to the formation of shaped products under pressure.

Table 2. Factors that determine the tensile strength of tablets.

Bonds	Low tensile strength	High tensile strength	
	Few weak bonds	Many weak bonds	Few strong bonds
Main mechanism of volume reduction			
Plastic	Large particles Low ductility No solid bridges	Very fine particles Particles of (micro-) rough surface Very plastic particles	Solid bridges formed
Plastic and brittle	-	Low elasticity	-
Brittle and elastic	Mainly elastic material	Mainly brittle material	-

Modified after [22,73].

fragmentation and plastic deformation facilitate interparticulate bond formation and as such have a direct effect on tablet tensile strength (**Table 2**).

4.1 Simulation

A number of methods have been proposed to simulate powder compression (for a review see [38]), mainly based on finite element (FE) [39,40] and discrete element (DE) [41] methods. However, it has been reported [42] that the implementation of the FE method is quite complicated, needs to be calibrated for each material and cannot generate information on the particle scale. It is advantageous to include the fact that plasticity of the material is density dependent [40]. The DE method is a simplified contact model and thus fails to give an accurate description of the particle deformation; furthermore, it is difficult to obtain stresses within individual particles [42]. Thus, a combined FE/DE method has been introduced to overcome these problems [42,43]. Ahmat *et al.* [44] described the compression event based on geometric modeling of solid flat-faced cylindrical pharmaceutical tablets interactively using a surface representation technique based on partial differential equations (PDEs) [45,46]. The

Table 3. Some commonly used parameterization methods.

	Equation	Derived parameter	Ref.(s)
Using force (pressure)–time curve evaluation			
Area comparison	Form of pressure–time curve as a measure of plasticity	[74,75]	[76]
Area comparison	Area ratio of compression–time and decompression–time curves as a measure of elasticity	[77,78]	
Weibull function	Degree of skewing and width	[79]	[80]
Frazer–Suzuki equation	Degree of skewing and width	[81]	[82]
Area–height ratio	Slope of compression–time curves	[83]	[84]
Using pressure and displacement vs time measurements			
Heckel	$\mathrm{In}\left(\frac{1}{E}\right) = kP + A$	$Py = 1/k$	[85-88]
Kawakita	$\frac{P}{C} = \frac{1}{ab} + \frac{P}{a}$ where $C = \frac{V_0 - V}{V_0} = \frac{H_0 - H}{H_0}$	a, $1/b$, ab	[89,90,35,91]
Shapiro	$\mathrm{In}(E) = \mathrm{In}E_0 - kP - fP^{0.5}$	f, k	[92,93,36]
3D model	$z = \ln\left(\frac{1}{1-D_{rel}}\right) = (t - t_{max}) \cdot (d + \omega \cdot (p_{\max} - p)) + (e \cdot p) + (f + d \cdot t_{max})$ where $d = \frac{\partial \ln\left(\frac{1}{1-D_{rel}}\right)}{\partial t}$ $e = \frac{\partial \ln\left(\frac{1}{1-D_{rel}}\right)}{\partial p}$ $f = \ln\left(\frac{1}{1-D_{rel}}\right)$	d, e, ω	[94,95]
Cooper-Eaton	$\frac{V_0 - V}{V_0 - V_\infty} = ae^{-k/p}$	a, k	[96]
Log-exp-	$V = V_1 - \omega \log(P) + V_e\, e^{\frac{p}{p_m}}$	ω, V_e, P_m	[97]
TWC (total work of compaction)	$TWC = \int_{x=0}^{x\max up} F_{up} \cdot dx_{up} + \int_{x=0}^{x\max lp} F_{lp} \cdot dx_{lp}$	*TWC [J]*	[98]

D_{rel}: Relative density; E: Porosity; E_0: Porosity of powder bed at time 0; F_{lp}: Force measured at lower punch; F_{up}: Force measured at upper punch; H: Height of powder bed at time t; H_0: Height of powder bed at time 0; P_m: Average pressure; P: Pressure; p: Pressure; p_{max}: Maximum pressure; t: Time; t_{max}: Time when pressure is back to 0; V: Volume of powder bed at time t; V_0: Volume of powder bed at time 0; V_∞: Volume at infinite time; V_1: Specific volume at a pressure of MPa; V_e: Volume at pressure 0; x: Positioning of punch (upper x_{up} or lower x_{lp}, respectively); $x_{\max up}$: Max. displacement of upper punch (absolute scale); $x_{\max lp}$: Max. displacement move of lower punch (absolute scale).

Table 3. Some commonly used parameterization methods (continued).

Equation	Derived parameter	Ref.(s)
NWC (net work of compaction) $NWC = \left(\int_{x=0}^{x\max up} F_{up} \cdot dx_{up} - \int_{x=x\max up}^{0} F_{up} \cdot dx_{up} \right) + \left(\int_{x=0}^{x\max lp} F_{lp} \cdot dx_{lp} - \int_{x=x\max lp}^{0} F_{lp} \cdot dx_{lp} \right)$	*NWC[J]*	[98]

D_{rel}: Relative density; E: Porosity; E_0: Porosity of powder bed at time 0; F_{lp}: Force measured at lower punch; F_{up}: Force measured at upper punch; H: Height of powder bed at time t; H_0: Height of powder bed at time 0; P_m: Average pressure; P: Pressure; p: Pressure; p_{max}: Maximum pressure; t: Time; t_{max}: Time when pressure is back to 0; V: Volume of powder bed at time t; V_0: Volume of powder bed at time 0; V_∞: Volume at infinite time; V_1: Specific volume at a pressure of MPa; V_e: Volume at pressure 0; x: Positioning of punch (upper x_{up} or lower x_{lp}, respectively); $x_{max\ up}$: Max. displacement of upper punch (absolute scale); $x_{max\ lp}$: Max. displacement move of lower punch (absolute scale).

PDE method can generate surfaces of complex geometries from a small amount of parameters. The Heckel plot obtained from the developed model showed that the model is capable of predicting the compaction behavior of pharmaceutical materials since it fitted the experimental data. A continuum mechanics model, represented by a force network between particles, can be related to the micromechanics of compression of granules. This approach also leads to satisfactory agreement between experimental data and prediction of the compression process in a confined space [47].

5. Parameters and evaluation

The press characteristic, that is, time–displacement function, of the punches given by the geometry of the machine, and as a consequence of the force (pressure) function, is important due to time-dependent deformation of particles in the tablet: at the same maximum pressure, tablets of widely different mechanical properties can be made. **Figure 3** shows a summary of some parameters that would affect the (mechanical) tablet properties beyond their composition. Numerous influence parameters lead to a confusingly large number of mathematical functions that may describe the compression event to a certain extent; however, none of them can correlate the process with the product in terms of mechanical properties of the tablet (not to mention its release properties) independently from a set of preset process parameters.

5.1 Single materials

In direct compression, the properties of the excipients are extremely critical for the tableting success. The choice of different commercially available materials is huge covering a large area of tableting behavior (design space). Moreover, even chemically identical materials in DC quality can have widely different properties. Prominent example of materials that are frequently used are lactose and microcrystalline cellulose [48]. For lactose, independently of the obvious differences due to chemical differences (α- and β-grades), crystallinity/amorphous content and pseudopolymorphism, there is a strong influence of particle size on deformation. Furthermore, for crystalline lactose qualities, manufacturing conditions such as crystallization and milling (brand-to-brand differences) and effects connected to particle surface properties may also cause different bonding properties [49,50]. For microcrystalline cellulose, similar significant differences for batch-to-batch and brand-to-brand variability have been described [18,51]. Such studies are of importance to estimate general limits of reproducibility of experiments with respect to the entire design space. It is important to notice that the interaction between particle size, specific surface area and packing behavior makes multivariate evaluation necessary even for single materials.

5.2 Optimized commercial excipients for direct compression: Coprocessed materials

Specific properties of a set of excipients can be synergistically combined and the advantageous effects (as compared with blending) may be surpassed by coprocessing, for example, spray drying, spray-congealing and micro-granulation of two or more materials. The aim is to produce ready-made 'one-body' excipients of invariant properties in terms of flowability, dilution potential (drug uptake capacity), tabletability and performance (in terms of tablet disintegration and drug release). Such multifunctional excipients (prominent and widely used examples are Ludipress® and Cellactose®) further simplify tablet manufacturing by direct compression. In the parameterization of the tableting behavior, coprocessed materials may be treated as single components in experimental designs.

5.3 Formulations (powder blends)

Application of experimental design (DoEs) makes it possible to extract maximum amount of information from the smallest number of experiment runs [52]. Screening designs, such as fractional factorial designs, are useful to single out the important parameters within an experimental setup. The disadvantage of

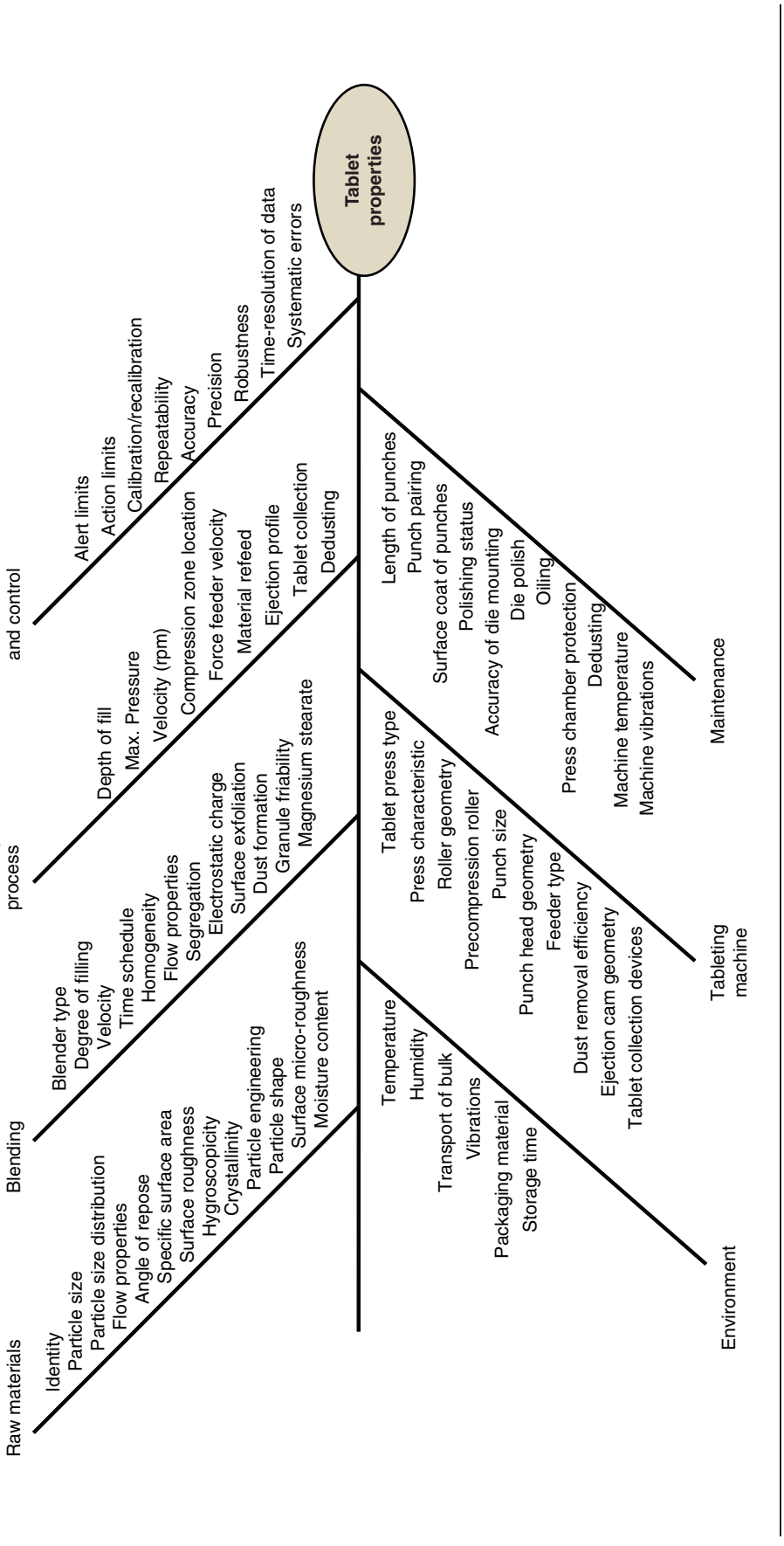

Figure 3. An overview over factors that may affect the mechanical properties of direct compression tablets.

highly fractionated designs is mainly the limited resolution of the models obtained; for example, it may not be possible to establish which of the investigated factors interact or show a nonlinear behavior. However, screening designs are valuable to identify the important factors that should be further studied in an optimization design. The central composite design is an example of a suitable design for the optimization of a formulation and/or process. This approach allows optimization of the important parameters also with respect to possible interactions and nonlinear behavior [52,53]. Many formulation optimization studies have been carried out in the industry and some of them were published (e.g., [9,53-57]).

The advantage of multivariate approaches, such as for instance multiple linear regression (MLR), principal component analysis and partial least square regression analysis (PLS) compared with univariate analysis, is the ability to identify and (for MLR and PLS) quantify possible interactions between variables and nonlinear behavior [55]. PLS models are able to handle colinearity and imbalance in the data matrix (e.g., due to missing samples) better than MLR and is thus widely used, also in direct compression formulations comprising numerous excipients (e.g., [51,54-57]). Another technique for identification of the most relevant parameters is using discriminant function analysis. In all modeling, care must be taken to avoid over-fitting of the calculated models.

For more thorough mechanistic studies, several authors have studied the compaction of binary mixtures [58-60]. It has been described that the densification and compaction behaviors of mixtures are influenced by the characteristics of the pure components and by the mass fractions of each component in the mixture. Both linear and nonlinear relationships have been observed between the compression parameters of the single materials and their proportions in the mixture. For ideal binary mixtures, Frenning *et al*. proposed a mixing law based on the Kawakita parameters [61]. Also other authors base their prediction models for the compressibility of binary mixtures on the Kawakita model [62]. These approaches show the ability to predict compression curves and Kawakita parameters, but the prediction of actual tablet properties remains unsolved.

Noncontinuous functions can be difficult to capture, even by studies based on central composite design. The percolation theory was introduced by Leuenberger to explain the mechanical properties of compacts and mechanisms of tablet formulation [63-65]. Percolation theory is a statistical theory that studies disordered or chaotic systems, where the components are randomly distributed in a lattice. A cluster is defined as a group of similar neighboring sites in a lattice. A percolating cluster is a cluster that extends throughout the lattice, that is, percolates the system. A tablet can be regarded as a heterogeneous binary (or higher) system consisting of a drug and an excipient. The sites in the cylindrical lattice (e.g., tablet) can be occupied by either the drug or the excipient(s). Depending on their relative volume ratio, one or both components may constitute a percolating cluster of particles. The percolating threshold of one of the components (drug or excipient(s)) indicates at which fraction this component dominates the system. This fraction is related to a sudden change in the properties of the system, that is, the system will be most affected by the percolating component. The percolating threshold is known as a critical point, where sudden changes in functionality (e.g., release mechanism) can occur. Also disintegration properties of tablets are a good example for this behavior [66]. Such noncontinuous functions are expected to be even more frequent in more complex formulations.

5.4 Influence of texture and lubrication

Properties of bulk materials strongly depend on the properties of the individual particles as well as the texture (orientation functions); both of these in turn depend not only on particle size but also on a former history of deformation (e.g., work-hardening, work-softening [29]). In terms of mechanical properties of the compacts, not only deformation based on particle properties such as crystal structure, crystal habit, surface roughness, moisture content, temperature, but also production parameters and handling contribute to the result. None of the models has up to now been able to capture these factors in a mechanistic way.

Furthermore, friction between the particles is a particular problem, which gives rise to mechanical failure of tablets during ejection due to lamination and capping. Instrumentation of the die wall quantifies the friction in preformulation setups; it may be possibly useful as a continuous control during high-speed tableting [67]. The standard procedure to reduce friction is to blend solid lubricants into the formulation. However, during this step, lubricant particles (e.g., magnesium stearate) scale off between the other components in a time-related and process-related manner (affected by cumulative shear strain, mixing order, etc.), whereby simultaneously the surface properties of the excipient particles change as well [68,69]. As a consequence, tablet properties are widely affected by the presence of low amounts of magnesium stearate and the blending procedure [68-70]. This may lead to noncontinuous changes and makes the prediction of tablet properties extremely difficult, although the lubrication step kept as little and constant as possible in systematic studies [49]. Additional literature on QbD considerations for lubrication in tablet formulation can be found in the recent review [71].

6. Conclusion and future aspects

A mechanistic understanding of the structure of the materials, basic properties and the effect of processing is necessary for meaningful use of DoE and PAT as formulation and process optimization tools. As illustrated above, for the analysis of direct compression processes, physical and physicochemical approaches to characterize the input materials (i.e., functional-related properties such as particle size,

powder flow, etc.), the process data (i.e., time-resolved force and displacement data and derived parameters) and the properties of the final product (i.e., tablet tensile strength, drug release, etc.) are combined. In the light of PAT, there is a need to move further from process analysis to process control, which ideally should be applicable in real time. Thus, evaluation of such concepts that open up for a possibility for process control tools is highly interesting. These are connected to online data acquisition of time-resolved force and displacement measurements during tableting. However, in addition to the fact that the compaction of powder beds is not fully understood on a mechanistic basis and these data cannot be directly interpreted, the tableting process occurs in a small volume, and the time frame of the event is very short (just a few ms). Both the dimension and time scales of tableting are considerably different from other processes that have already come longer on their way toward process control, such as powder mixing, granulation and film coating. Hence, the process control of a powder compaction operation still represents a challenging issue from this point of view as well. Physical measurements (stress, strain) seem to be a more convenient strategy to control a compaction process rather than the use of physicochemical methods (spectroscopy, etc.).

Nordström and Alderborn have suggested using the degree of compression as a potential process tool for tablet tensile strength [72]. By straining the powder bed during tableting, they assessed the degree of bed compression, which correlated to the tensile strength of the final product. This approach requires a new tablet machine design and instrumentation allowing the compression event to be interrupted at a predetermined straining of the powder bed. A technology giving direction toward predetermined straining of the powder is the pressure-restricted mounting of the punches that has been used in some tableting machines (air compensator; www.courtoy.be). However, to our knowledge, there are no independent studies about the advantages of such setup regarding the rational formulation of direct compression tablets.

7. Expert opinion

At this point, we conclude that the compression step of a single, crystalline and well-characterized material (e.g., in terms of particle size, particle size distribution, particle shape, surface properties) is a particular fast and complex process compared with other pharmaceutical production processes. This sets high requirements on the data acquisition technology, in order to yield the process data in high precision and accuracy, which is essential for reasonable parameterization of the force and displacement (porosity) functions. The current developments in the fields of sensors and computing will have large impact on the data quality in the nearest future. However, this may not solve the problem of a thorough description of the compression event, because tablets are not homogeneous nor continuous, and particle properties depend on many other parameters, such as shape, orientation and pre-experienced stress. Classical methods of experimental design are still useful: in screening setups, general trends may be found by comparing different materials within the same experimental series (i.e., system of compression profiles) while as many process parameters as possible are kept constant. Even fractional designs for screening may be used; there is a high probability to find descriptors that are connected to practical experience for the most obvious relationships. For optimization, the design space will be restricted to the most interesting areas found in the screening.

The benefit of multivariate designs is to cover many more parameters in the same models. However, if they should be extended to predictive abilities, a more thorough understanding of the physical processes is still needed. For such mechanism-based evaluation of the contribution of the materials, sequential handling of different approaches will be useful based on the physical processes that are involved in order to single out the different overlapping effects.

Up to now, powder blends are even less understood in terms of prediction of tablet properties than single materials, although this is an important step toward better formulations. Prediction of properties is even more difficult in the presence of lubricants, in particular magnesium stearate, because the blending conditions have large impact, as well as interaction with the respective materials contained in the formulation.

The immediate and most obvious goal of evaluation of compression properties is the rational development of directly compressed tablets based on predictive models; just this process would yield the optimum tablet at all (in contrast to empirical approaches), save material and time. In addition, the impact on process control is obvious, with the perspective of possible real-time release (parametrical release) of the tablets, which in addition to time saving may include a decreased risk of releasing outliers. Furthermore, the better understanding of the processes may also lead to the development of new and smarter directly compressible materials, not restricted to mechanical properties of the tablets but extending in terms of drug uptake capacity, flow properties and so on. We see already today a trend toward the use of processed (e.g., spray-dried) materials and coprocessed compound excipients. As a next step, process and machine parameters may to a larger extent become flexible by the development of new technologies, which in turn would enable us to systematically optimize and tailor-make the compression profiles according to material properties.

Due to the discussed nonhomogeneity and non-isotropic properties of powder beds and tablets, three-dimensional (3D) models of more complex structure (more complex than the currently used FEs and DEs) may be needed to describe the processes in more detail. A better and more detailed understanding of material properties under

(confined) pressure may be used to extend the models to processes when the tablet is in contact with water. By this, the rational formulation of drugs not only in terms of tabletability but also in terms of certain dissolution properties may be covered.

For the nearest future, we would expect direct compression to remain the standard technology for mass production of tablets due to its high productivity and cost-effectiveness. However, novel technologies (in the first place advantageous regarding individual dosing), such as soaking porous inert shaped products or 3D printing technologies may catch up for the mass market, if they should turn out to be as cost-effective as direct compression.

Declaration of interest

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