Arh. farm. 2022; 72: 637 – 660 *Review article/Pregledni rad*

Mathematical approaches for powders and multiparticulate units processability characterization in pharmaceutical development

Ivana Vasiljević*, Erna Turković, Ivana Aleksić, Jelena Parojčić

University of Belgrade – Faculty of Pharmacy, Department of Pharmaceutical Technology and Cosmetology, Vojvode Stepe 450, 11221 Belgrade, Serbia

*Corresponding author: Ivana Vasiljević, E-mail: ivanav@pharmacy.bg.ac.rs

Abstract

An understanding of material properties and processing effects on solid dosage forms performance is required within the Quality-by-design approach to pharmaceutical development. Several research groups have developed mathematical approaches aiming to facilitate the selection of formulation composition and the manufacturing technology. These approaches are based on material particulate, bulk and compression-related properties. This paper provides theoretical assumptions and a critical review of different mathematical approaches for processability characterization of powders and multiparticulate units.

Mathematical approaches have mainly been developed for directly compressible materials, but sometimes other manufacturing technologies, such as roller compaction and wet granulation, are also considered. The obtained compact tensile strength has been implemented in the majority of approaches, as an important characteristic describing compact mechanical properties. Flowability should be also evaluated, since it affects sample processability. Additionally, particle size and shape, material density and compressibility, compactibility and tabletability profiles have been also distinguished as relevant properties for solid dosage form development.

The application of mathematical approaches may contribute to the mechanistic understanding of critical material attributes and facilitate dosage form development and optimization. However, it is essential to select the appropriate one, based on the intended dosage form characteristics, in order to ensure that all relevant powder/multiparticulate units characteristics are implemented and critically evaluated.

Key words: drug manufacturing, solid dosage forms, tensile strength, flowability, material classification

https://doi.org/10.5937/arhfarm72-40961

Introduction

The implementation of the Quality by Design concept in pharmaceutical development has set increasing expectations for understanding the impact of material properties and process parameters on drug product performance. Dosage form development is shifted from a conventional trial-error approach to knowledge-based pathways, directing formulation and manufacturing route selection. Due to a diverse portfolio of excipients available on the market, formulation scientists are faced with challenges regarding excipient type and concentration selection, in order to achieve the desired dosage form properties and bioavailability. There is a tendency for defining the design space, determined by critical material attributes and critical process parameter ranges, using mathematical relationships. The Food and Drug Administration (FDA) recognized the need for mechanistic understanding of active pharmaceutical ingredients (APIs), excipients and manufacturing process effects on the final product, in order to rationalize excipient choice and reduce the amount of experimentally tested formulations (1). These observations resulted in increased research efforts towards a comprehensive evaluation of drug/excipients mixtures affecting the final dosage form performance. Several research groups introduced mathematical approaches, i.e. material classification methodologies, considering particle properties, powder bulk properties, compression behavior and the characteristics of the obtained compacts, in order to provide better insight into the relationship between critical material attributes and the obtained solid dosage form properties (2–6). These approaches are based on a combination of powder particulate, bulk and compression-related properties.

The mathematical approaches intended for a better understanding of powder properties which have been described in the literature may be divided into two groups, depending on the parameters implemented (Figure 1):

- expert systems based on a combination of powder particulate, bulk and compression-related properties (particle size and shape, density, powder flow, etc.): Manufacturability Classification System (2); Expert System for Drug Development, i.e. SeDeM Expert System (3), and
- expert systems based on powder compression behavior (yield pressure, compact tensile strength, ejection stress, etc.): Classification system for tableting behavior of binary powder mixtures, i.e. Tabletability Classification System (4); Classification system based on tableting properties (5); Compression behavior classification system (6).

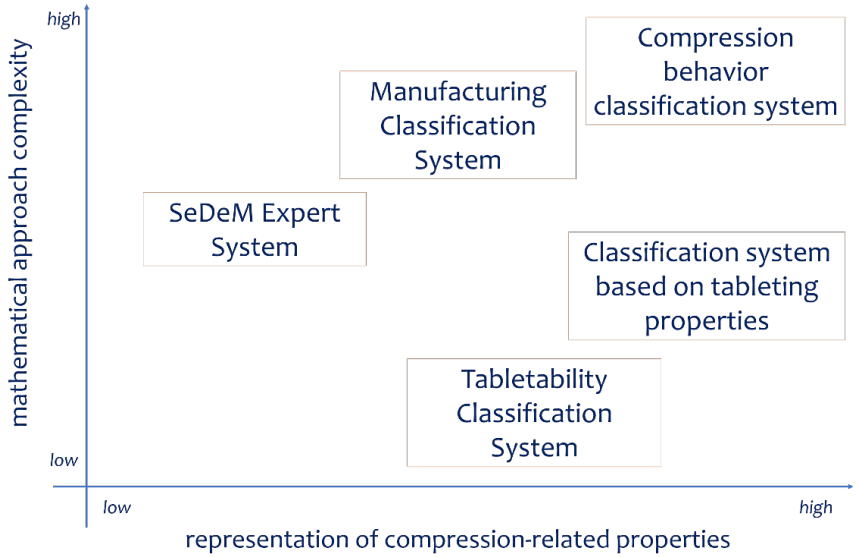

Figure 1. **The differences between complexity and parameters included in the mathematical approaches for powders and multiparticulate unit characterization described in the literature (adapted from references 2-6)**

Slika 1. **Razlike u složenosti i parametrima opisanim u okviru različitih matematičkih pristupa za karakterizaciju praškova i višečestičnih sistema (prilagođeno prema referencama 2-6)**

The aim of this paper was to provide a comprehensive review and analysis of the benefits and limitations of mathematical approaches intended for processability evaluation and solid dosage forms development.

Expert systems based on a combination of powder particulate, bulk and compression-related properties

Manufacturability Classification System

Manufacturability Classification System (MCS) is a pharmaceutical development tool intended for the assessment of material manufacturing suitability (2). The MCS framework is based on information regarding the properties of the API incorporated, the intended dosage form and the chosen manufacturing process (2, 7). In the MCS framework, APIs are classified into four groups, according to their suitability for processing:

- MCS Class 1: APIs suitable for direct compression,
- MCS Class 2: APIs suitable for dry granulation,
- MCS Class 3: APIs suitable for wet granulation, and
- MCS Class 4: APIs which may be incorporated in dosage forms manufactured using complex technologies, e.g. melt granulation, liquid or semi-solid capsule filling, inert core coating, etc. (2).

Each MCS Class was assigned a list of relevant API properties and favorable limit values, as represented in Table I (2, 7-11). The number of pre-defined API properties and their limit value rigidity decreases from MCS Class 1 to MCS Class 4. Therefore, the manufacturing technologies within MCS Class 3 and, particularly, MCS Class 4, may be suitable for APIs exhibiting a wide range of properties, since these manufacturing technologies may compensate the unfavorable properties of the APIs. On the other hand, the complexity and time-consuming character of manufacturing technologies increase from MCS Class 1 to MCS Class 4. For example, direct compression, as the simplest process, is performed in two stages – mixing and compression, which is favorable due to lower costs and time investment. However, the APIs intended for direct compression must fulfil a list of demanding requirements, such as high tableting performance and good compact mechanical properties (2, 8-9).

MCS-based material characterization provides comprehensive insight into powder properties, i.e. particle properties, powder bulk and compression-related parameters affecting the manufacturing process. It was based on a wide range of API properties, relevant for dosage form development: dose, particle size, morphology, surface area, solid state form, powder blend flow, segregation tendency, compression behavior, including compact mechanical properties (7). Additionally, the MCS takes into account the percolation threshold, representing the lowest API ratio at which its properties begin to impact the finished dosage form properties. Visual risk representation tools, such as parallel coordinate plots or radar charts, as well as risk calculation based on the relevant API characteristics and targeted dosage form attributes, are recommended within the MCS framework quantitative tool aid (7).

Table I *Manufacturability Classification System* parameters and parameter limits relevant for different manufacturing technologies (adapted from references 2, 8-9)

Tabela I Parametri i opseg vrednosti parametara opisanih u okviru *Sistema za klasifikaciju materijala prema pogodnosti za proizvodnju*, od značaja za različite metode izrade tableta (prilagođeno prema referencama 2, 8-9)

DIRECT COMPRESSION		
Property	**Parameter**	**Limit value**
Particle size and shape	D4,3 (mean volume diameter)	>80 μm
	D10 (10^{th} percentile diameter)	>30 μm
	D90 (90^{th} percentile diameter)	≤1000 μm
	Aspect ratio	<1.5
Blend uniformity	Blend potency	<2% relative standard deviation
Powder flow	Effective angle of internal friction	<41°
Powder density	True density	1.0–2.5 g/ml
	Bulk density	>0.5 g/ml
Tableting performance	Dwell time sensitivity	Low
	Precompression force	Low
	Compression stress (at ~0.85 solid fraction)	20–125 MPa
Compact mechanical properties (at ~0.85 solid fraction)	Tensile strength	>1.0 MPa
	Brittle fracture index	<0.2
	Indentation hardness	75–250 MPa

ROLLER COMPACTION		
Property	**Parameter**	**Limit value**
Compactability	At 0.7 solid fraction	>1 MPa
Loss of compressibility	Compressibility remaining in granules	>1.7 MPa
Bulk density	At>0.14 solid fraction	>0.2 g per ml
Wall friction	Angle of wall friction	<20 degrees
Flow assessment	Flow function coefficient	>4
	Carr index	<35%
Solid State Properties	Melting point	>90 ºC
	Glass Transition (Tg)	>90 ºC
	Loss of crystallinity during compaction	None
Particle size for content uniformity	Blend potency	Meets Rohr's criteria [10]
Stability with excipients	Acceptable Stability	>2 years at room temperature [11]

WET GRANULATION (WG)				
Property	**Condition**	**Drug loading**		
		Low	**Medium**	**High**
Low density			Driver for WG	Driver for WG
Poor wettability		Driver for WG	Driver for WG	Driver for WG
Moisture sensitivity		High risk	High risk	High risk
Morphology	Plates	Low risk	Medium/High risk	High risk
	Needles	Low risk	High risk	High risk
	Equant	Low risk	Low risk	Low risk
Deformation mechanism	Elastic	Low risk	Low/Medium risk	Medium/High risk
	Plastic	Low risk	Low risk	Low risk
	Brittle	Low risk	Low risk	Low risk
Solubility interaction	Binder interaction aids release	Low risk	Low risk	Low risk
	Binder interaction slows release	Low/Medium risk	Medium risk	High risk
Polymorph/Hydrate formation		Medium/High risk	Medium/High risk	Medium/High risk
Melting range	<90 ºC	Low risk	Low/Medium risk	Medium/High risk
	>90 ºC	Low risk	Low risk	Low risk
Poor flow		Driver for WG	Driver for WG	Driver for WG
High tendency to segregate		Driver for WG	Driver for WG	Driver for WG

Leane et al. (12) conducted a survey among people working in the pharmaceutical industry in order to assess the applicability of the MCS in pharmaceutical development. Particle size and drug load were most frequently stated as API properties impacting the ease of manufacture. Other relevant parameters noted in the survey were: particle shape, physical and chemical stability of the API, including compatibility with excipients, bulk and tapped density, mechanical properties such as particle hardness and yield pressure, i.e. the stress at which the material begins to deform irreversibly, surface properties such as cohesion/adhesion, wettability, surface energy and surface roughness, crystal properties such as packing and hygroscopicity (12). Based on the survey results, Leane et al. emphasized the API dose, representing the drug load in the solid dosage form, and API Biopharmaceutical Classification System (BCS) class, as critical formulation parameters (12). The relationship between the BCS Class and particle size was described: in the case of poorly soluble APIs, i.e. BCS Class 2/4, particle size is usually controlled and more complex manufacturing processes are often required, due to the poor compression behavior of smaller particles.

The MCS framework represents a comprehensive mathematical approach, since it is based on both compression-related parameters, relevant for compression process and obtaining compacts with good mechanical properties, and powder properties affecting the manufacturing process, such as particle size and shape and flowability. It may contribute to targeted API particle engineering for the intended manufacturing process and dosage form (12). Generally, the MCS may be expanded and it may be applied to different systems, e.g. powder blends, multiparticulate units, etc. In these cases, an adjustment of some parameter limits, e.g. particle size limits, may be required, according to the specific material and intended dosage form. Some of the parameters included in the MCS framework, such as the brittle fracture index or indentation hardness, cannot be obtained by routine powder characterization. However, Leane and Pitt stated that the relationships between compression pressure, compact solid fraction and compact tensile strength, i.e. compactibility, compressibility and tabletability profiles, may be used for compression suitability evaluation (13). The comprehensive characterization denoted in the MCS framework may be used as a detailed guideline for accelerating solid dosage form development.

Expert System for Drug Development

The Expert System for Drug Development, i.e. SeDeM Expert System (Span. *Sistema Experto para DEsarrollo de Medicamentos*) represents a framework intended to: i) assess powders' (APIs, excipients and powder blends) suitability for direct compression, ii) identify the powder properties which should be improved for compression, and iii) suggest the most suitable excipient/excipients and their ratios, with the aim of obtaining compressible formulations and tablets with adequate mechanical properties and disintegration (3). Parameters included in the SeDeM Expert System framework are divided into 5 groups, named incidence factors. Each parameter is assigned to desirable limits, as represented in Table II (3).

Table II *SeDeM Expert System* incidence factors, parameters, limit values and mathematical transformation (adapted from reference 3)

Tabela II Parametri, opseg vrednosti parametara i matematičke transformacije opisane u okviru *SeDeM* ekspertskog sistema (prilagođeno prema referenci 3)

Incidence factor	Parameter (P)	Limit value	Mathematical transformation
Density	Bulk density (ρ_b)	0 – 1 g/ml	10P
	Tapped density (ρ_t)	0 – 1 g/ml	10P
Flowability	Hausner ratio (HR)	1 – 3	(30-10P)/2
	Flowability (f)	0 – 20 s	10 – P/2
	Angle of repose (α)	0 – 50 °	10 – P/5
Compressibility	Inter-particle porosity (Ie)	0 – 1.2	10P/1.2
	Carr index (CI)	0 – 50 %	P/5
	Cohesion index (Icd)	0 – 200 MPa	P/20
Particle Size	Fines fraction (Pf)	0 – 50%	10 – P/5
	Homogeneity index	$0 – 2 \bullet 10^{-2}$	500P
Stability	Moisture content (MC)	0 – 10 %	10 - P
	Hygroscopicity	0 – 20%	10 – P/2

The implementation of 12 parameters is suggested within the framework, whereas 8 parameters represent the minimum, but more parameters may be added depending on the formulation challenges and requirements. After powder characterization, each parameter is mathematically transformed into a radius parameter, ranging from 0 to 10, where the higher value indicates favorable powder properties. Radius parameters may be represented as a radar chart, i.e. SeDeM Diagram (3). The obtained chart is a useful visual aid in powder/powder blend characteristics assessment and insight into compression suitability. When all radius parameter values are equal to 10, the SeDeM Diagram forms a circumscribed regular polygon. Dai et al. (14) reported that the SeDeM Expert System contributes to MCS, enhancing the distinction between powder blends suitable for direct compression, i.e. Class 1, and other manufacturing processes. They stated that the SeDeM Diagram provides a quick overview of manufacturing risk levels and aids in the identification of impaired powder characteristics, which may impair the compression process (14). Additionally, radar charts, implemented in the SeDeM Expert System, are recognized in the MCS as a quantitative visual assessment tool (2).

Apart from powder characterization, SeDeM Expert System provides an additional aid regarding the identification of optimal compressible diluents for a selected API and calculation of the appropriate excipient content in the powder blend, using the following Equation (1):

$$CE = 100 - \frac{RE-R}{RE-RD} \cdot 100, \quad (1)$$

where CE represents the concentration of the diluent to be mixed with the model drug, RE represents the excipient mean radius value, R represents the mean radius value to be obtained in the powder blend (usually equal to 5, as the minimal acceptable incidence factor value), and RD represents the mean radius value of the model drug which should be improved (15).

First attempts of SeDeM Expert System implementation were focused on compressible excipients evaluation and comparison, particularly diluents and disintegrants (15–17). Recently, Scholtz et al. (18) investigated the SeDeM Expert System suitability for compressible formulation development and obtaining tablets with low weight variation and suitable mechanical properties. Three model drugs (pyridoxine hydrochloride, paracetamol and furosemide) and seven excipients (microcrystalline cellulose (Avicel® PH200), calcium hydrogen phosphate dihydrate (Emcompress®) and lactose-based co-processed excipients (Tablettose® 80, FlowLac® 100, Cellactose® 80, MicroceLac® 100, StarLac®)) were used in the study. The authors stated that SeDeM Expert System characterization may detect inconsistencies between different excipients and APIs batches and that it enabled forecasting the API and excipients content in the formulation, required for compressible formulations development, without physically producing the tablets. This is highly beneficial in terms of time- and material-saving. However, several SeDeM Expert System limitations were emphasized in the study: i) some relevant API properties were neglected, such as elasticity and the cohesive behavior and the consequential decrease in powder flow; ii) the ability of novel co-processed excipients, intentionally developed for direct compression, to overcome API limitations. In certain cases, SeDeM-based predictions led to successful formulations, whereas in the majority of the samples studied the obtained powder blends exhibited either low flowability or high compact friability (18). The authors suggested the SeDeM Expert System Equation (1) as a general guideline for the compressible diluent ratio. However, it was necessary to adjust the excipient ratio, increasing it in a stepwise manner, by 5%, in order to obtain a compressible formulation. In spite of more effort and time invested, this approach was found to be advantageous for pharmaceutical development and achieving the optimal formulations.

Due to its flexibility and routine powder characterization methods, SeDeM Expert System was extensively investigated and applied with different objectives. One of its modifications is the SeDeM-ODT Expert System, intended for facilitating orodispersible tablet (ODT) formulation development. Apart from parameters and incidence factors suggested in the SeDeM Expert System, *Disgregability* is added as an additional incidence factor, based on a disintegration test for effervescent tablets and compendial disintegration test described in the Pharmacopoeia, with or without using discs (19). The disintegration time obtained by these methods may not be relevant for ODTs, since different method modifications and stricter criteria have been adopted, i.e. ODTs should disintegrate within 30 s (20). However, it was reported that the SeDeM-ODT Expert System was helpful for identifying unacceptable formulations for direct ODT compression, which reduced the time and financial costs in both preformulation and

formulation phases (21–23). Rao et al. (23) performed a SeDeM-ODT Expert System-based analysis for the development of solid dispersions with a low soluble API, subsequently incorporated in the ODT formulation. The SeDeM-ODT Expert System framework facilitated the identification of excipients with favorable compressibility, enabled compressible diluent ratio calculation for obtaining compressible formulation and obtaining tablets with adequate hardness, friability, disintegration time and dissolution profiles (21–23).

Another SeDeM Expert System modification was applied to compressed chewing gum development (24). The authors stated that the formulation was successfully compressed, even though the SeDeM Expert System predicted unacceptable compression properties. It was recognized that powder blends exhibited non-linear behavior, which is not considered within the SeDeM Expert System. In the case of compressed chewing gums, additional parameters should be added to the SeDeM Expert System diagrams, in order to ensure successful formulation development, such as friability, indicating tablet mechanical properties, and chewability, as the critical quality attribute of compressed chewing gum (24).

Shah et al. (25) modified the SeDeM Expert System in order to obtain an expert system suitable for liquid carrier/adsorbent characterization, i.e. the SeDeM-SLA (Solid-Liquid Adsorption). They replaced the *Loss on drying* by *Percent of oil spontaneously released*, while the *Cohesion index* was replaced by *Adsorption capacity*, i.e. the ratio between oil and carrier amount in the mixture. It was found that the SeDeM-SLA Expert System represents a useful tool for carrier selection, superior to the conventional trial-error approach (25). Similarly, Mamidi et al. (26) applied the SeDeM Expert System framework in order to identify the most suitable diluent for liquisolid formulation. They suggested the the SeDeM Expert System extension with compressibility and compactibility-related parameters, namely *Mean yield pressure* (50-300 MPa) and *Compactibility parameter*, obtained by fitting the data to the Leuenberger equation (0-5 MPa) (27). The SeDeM Expert System was helpful in the selection of the most suitable excipients during preformulation, which is particularly advantageous for narrowing the choice of directly compressible excipients available on the market. The authors emphasized the diluent selection complexity and suggested the percolation theory application alongside the SeDeM Expert System (26). This would provide complementary prediction and more accurate design space estimation, as reported by Galdón et al (28).

One of the major advantages of the SeDeM Expert System are simple and common characterization methods included, which are widely available in research and development laboratories. It is easy to implement additional parameters, depending on the powder and final dosage form properties, such as the *Percent of oil released spontaneously*, *Adsorption capacity*, *Mean yield pressure* and *Compactibility parameter* etc (25-26). Some parameters included in the SeDeM Expert System are interdependent, e.g. bulk and tapped density are used for Hausner ratio, Carr index and inter-particle porosity calculations. Favorable materials, according to the SeDeM Expert System,

exhibit a low Hausner ratio, as a flowability parameter, and a very high Carr index (even close to 50), as a compression-related parameter. This parameter value combination is not achievable, since Carr index and Hausner ratio values exhibit the same trend. Some parameter limits suggested should be further analyzed and revised. For example, powder flow is expressed for a 100 g sample, but it may be lowered to 40 g, as suggested by Gülbağ et al. (29), to obtain relevant data, particularly when the amount of the sample available is limited. Compact hardness (0-200 N) could be replaced by compact tensile strength, which is a more standardized parameter describing mechanical properties and enabling comparison between compacts of different sizes. The tensile strength value is suggested to be higher than 1.0 MPa (mild criterium) or 1.7 MPa (strict criterium) (30–31). It is considered that high tensile strength, at a solid fraction of 0.85-0.9, indicates that compacts are robust to further processing such as film coating, packaging, transport and handling by the patient (30-31).

The parameters included in the SeDeM Expert System are comprehensive and describe a wide range of material properties; therefore, particle size and flowability impacts are not neglected. The SeDeM Expert System database provided by the excipient manufacturer would aid the preformulation scientist in the selection of the most suitable excipient, based on the selected API parameters, reduce the number of experiments and shorten the preformulation stage (26). However, in order to obtain directly compressible formulations, material compression behavior and compact mechanical properties should be more thoroughly investigated and emphasized, since sample compactibility, compressibility and tabletability are neglected.

Expert systems based on compression-related parameters

Tabletability Classification System for binary powder mixtures

Sun et al. (4) developed the *Classification system for tableting behavior of binary powder mixtures*, i.e. *Tabletability Classification System (TCS)*. It is intended for binary powder blends assessment, based on the relationship between powder fraction in the blend and compact tensile strength, obtained at a constant compression pressure. It should provide a better understanding of powder interactions in the mixture and classify powder mixtures into three types and fifteen sub-classes (4):

- *Type I* behavior indicates that the powder blend components may be individually compressed into compacts with tensile strength higher than zero, and their tensile strength values differ by more than 10%. The majority of filler-binder binary mixtures exhibit Type I behavior. Type I is subsequently divided into seven sub-classes: *Type I(a)* blends, which exhibit a tablet linear relationship between tensile strength and weight fraction; *Type I(b)* and *I(c)* powder blends exhibit mild and severe positive deviations, respectively, from an ideally linear relationship between tensile strength and weight fraction; *Type I(d)* and *I(e)* powder mixtures exhibit mild and severe negative deviations, respectively, from the linear relationship between tensile strength and weight fraction; *Types I(f)*

and *I(g)* are characterized by a constant tablet tensile strength (at either low or high end of the curve) over a certain weight fraction of the mixtures.

- *Type II* behavior is represented when the tensile strengths of powder blend components compacts are approximately the same (less than 10% difference) and it is divided into three sub-classes: *Type II(a)* is the ideal case where powder mixture does not affect tablet tensile strength; *Type II(b)* behavior is characterized by higher powder blend tablet tensile strength in comparison to the tensile strength of a single blend component; in the case of *Type II(c)*, tablet tensile strength of powder blend is always lower than the tablet tensile strength of a single component.
- *Type III* behavior is characterized by zero bonding propensity of powder blend components, i.e. when a mixture contains a powder with limited tabletability up to a critical concentration. In this case, the binding propensity within the same type of particles is negligible. The maximal powder concentration in the mixture, which does not prevent obtaining compacts with acceptable mechanical properties, is specified by the percolation theory. Five sub-classes may be distinguished within *Type III*: *Type III(a)* exhibits an ideal linear behavior between the critical point and pure powder; *Type III(b)* and *III(c)* exhibit positive and negative deviations from the ideal line, which is relevant for compressible tablet formulation development with poorly compressible APIs; *Type III(d)* behavior is identified if the tensile strength of the mixture exceeds the tensile strength of a mixture component; *Type III(e)* is a special case of *Type I(f*), where the powder blend component does not form an intact tablet under the given pressure and the addition of another blend component does not significantly deteriorate its tensile strength until a critical amount is reached.

The authors stated that the consistent application of the suggested *Tabletability Classification System* would provide a better understanding of model drug and excipient mechanical properties and facilitate the development of binary mixtures compacts, with good mechanical properties (4). One of the TCS limitations is that powder blends prepared for tablet manufacturing usually consist of more components, apart from the diluent and API, required to obtain adequate compacts (e.g. disintegrants, lubricants, antiadhesives etc), which also affects the final compact properties.

Classification system based on tableting properties

Osamura et al. (5) introduced the *Classification system based on tableting properties,* based on powder compression behavior: i) compressibility, estimated as the bulk density change in the powder bed during compression, ii) compactability, reflecting the particle binding under compression pressure applied, and iii) manufacturability, indicating the ease of compaction, e.g. friction forces between the compact and die wall which cause material sticking and compact failure. The classification based on tableting properties emphasized two critical parameters: compact tensile strength, reflecting

material compactibility, and ejection stress, reflecting manufacturability. Tensile strength of 2 MPa or higher is recommended, while ejection stress should be 5 MPa or lower, in order to obtain easy compaction and transportation to the end-user (30-31). Osamura et al. (4) plotted the graph, reflecting tensile strength (lower or higher than 2 MPa) and ejection stress (lower or higher than 5 MPa), dividing the materials into 4 Classes (Figure 2):

- Class I: good "Compactability" and "Manufacturability" (e.g. microcrystalline cellulose),
- Class II: poor "Compactability" and good "Manufacturability",
- Class III: good "Compactability" and poor "Manufacturability" (e.g. spray-dried lactose, spray-dried mannitol), and
- Class IV: poor "Compactability" and poor "Manufacturability (e.g. fine powder lactose monohydrate, fine powder mannitol, granulated lactose, granulated mannitol)

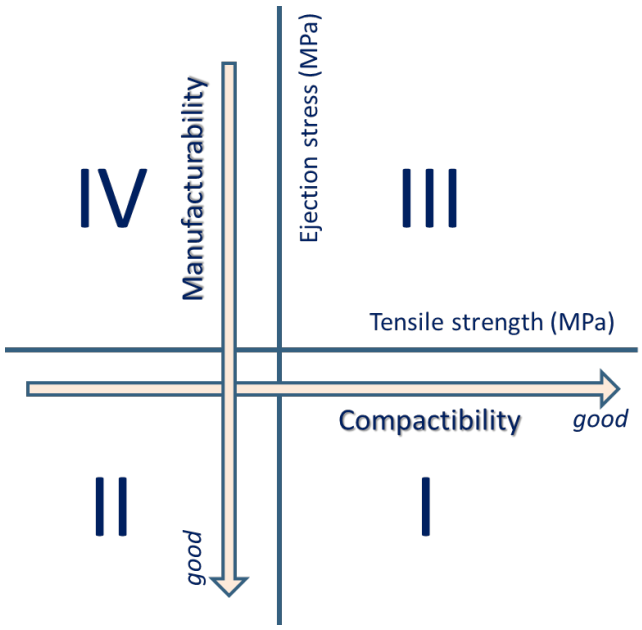

Figure 2. Classification system based on tableting properties (adapted from reference 5)
Slika 2. Sistem za klasifikaciju zasnovan na svojstvima pri tabletiranju (prilagođeno prema referenci 5)

The plot provided an easier visual interpretation of powder tableting properties and its implementation led to reduced compaction failures. Additionally, the plot facilitated the identification of formulation limitations and accelerated the scale-up process. The authors stated that the plot obtained may be used for solving compact deficiencies, such as sticking, capping and lamination (5).

Compression behavior classification system

Compression behavior classification system (CBCS) was developed as an expert system for directly compressible powders, based on the knowledge regarding compression mechanics (6). CBCS was based on the implementation of powder compression models, i.e. Kawakita, Shapiro and Heckel equations (32–36). The Kawakita equation describes the relationship between compression pressure and powder volume and distinguishes two parameters: i) *a*, which is equal to the initial powder porosity in the die, and ii) *b*, which is related to the resisting forces in the case of compression (33).

Nordström et al. (33) investigated the relationship between particle size and Kawakita parameters. They reported that fine particles, usually prone to significant particle rearrangement at low compression forces, exhibit low values of parameter b^{-1} and high values of *a*. They proposed the implementation of the relevant Kawakita parameters ratio, parameter ab^{-1}, as the overall indicator of the particle rearrangement contribution to the powder compression profile. In the case when particle size is lower than 40 μm, particle rearrangement is significant and notably impacts the compression profile (33).

Klevan et al. (34) investigated the compression parameters derived from commonly used powder compression models, Kawakita, Shapiro and Heckel equations. They investigated seventeen powders, both APIs and excipients, exhibiting different particle size and shape, mechanical properties and compression behavior. The results obtained indicated that a combination of the selected compression parameters could be utilized to identify relevant differences in compression behavior for a wide range of materials, and that this information may be evaluated in an efficient way by applying multivariate data analysis techniques.

CBCS is based on compressibility, compactibility and tabletability descriptors (6) (Figure 3). In the first step, the compression profile according to the Kawakita equation is developed (35). In the case when particle rearrangement notably affects compression process, powder exhibits low values of b^{-1} and high values of parameter *a*. Powders with $ab > 0.1$, $a > 0.6$ and $b^{-1} < 7$ are classified into Class I, while powders with $ab < 0.1$ belong to Class II. In the second step, the compression profile is fitted to Shapiro equation (34) and Class II is divided into ductile materials, i.e. type IIA ($f > 0.1$), or brittle materials, type IIB ($f < 0.1$), indicating the extent of particle fragmentation during compression. In the third stage, the Heckel equation is used for reflecting porosity-compression pressure relationship (36). Yield pressure obtained from the Heckel equation indicates the material propensity for plastic deformation and was used to classify materials from very soft to hard. In the fourth step, the Ryshkewitch-Duckworth equation is applied to describe powder compactibility (37-38) and the obtained parameters indicate the particles bonding capability. The materials are classified as easily compacted (Type E, $k_b < 10$) and compacted with difficulty (Type D, $k_b > 10$).

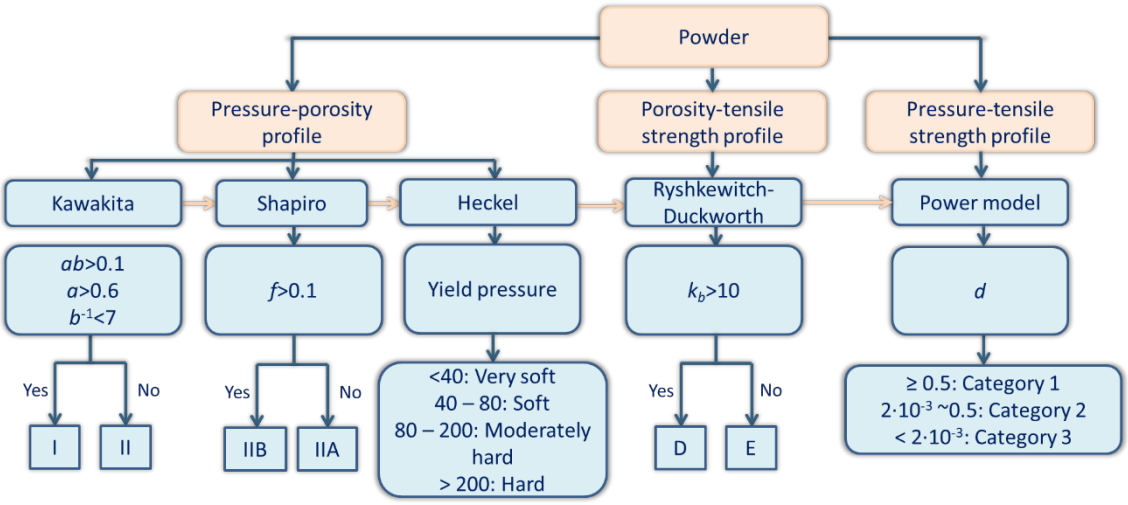

Figure 3. ***Compression behavior classification system*** **decision tree (adapted from reference 6)**

Slika 3. **Stablo odluke, prikazano u okviru** ***Sistema za klasifikaciju prema kompresivnim svojstvima*** **(prilagođeno prema referenci 6)**

Dai et al. (6) implemented a tabletability assessment step in the CBCS, based on the newly suggested parameter d. Materials with excellent tabletability belong to Category 1 ($d \geq 0.5$). Category 2 ($2 \cdot 10^{-3} \leq d < 0.5$) is subdivided into: i) 2A - powders with acceptable tabletability (compact tensile strength $>$2.0 MPa) at a low to middle compression pressure (50–100 MPa), while having good tabletability (compact tensile strength > 3.0 MPa) at middle to high compression pressure (100–150 MPa), ii) Category 2B powders exhibit acceptable tabletability only at a middle to high compression pressure (100–200 MPa), and iii) Category 2C powders, with unacceptable tabletability over the full pressure range (< 200 MPa). Materials in Category 3 ($d < 2 \cdot 10^{-3}$) exhibit unacceptable tabletability even at a high pressure range (150–200 MPa). Category 2A and 2B powders require fine compression pressure adjustment. Category 2C and Category 3 powders may be directly compressed, but compact mechanical properties may be impaired as the percolation threshold is approached (39).

The main advantages of all expert systems based entirely on powder compression behavior (Classification system based on tableting properties, Classification system for tableting behavior of binary powder mixtures, i.e. Tabletability Classification System, Compression behavior classification system) is that a small material amount is required for obtaining thorough data and complex compression-related models and parameters. The benchtop compaction simulators used in the investigations are user-friendly and the supporting software enables easy data extraction. However, the data obtained needs to be fitted into complex equations, which require thoughtful parameter estimation and analysis. The main limitation of expert systems entirely based on powder compression

behavior is diminishment of material properties effects relevant for processing, e.g. particle size and size distribution, particle shape, powder density and flowability.

Applicability of expert systems in multiparticulate units characterization

Multiparticulate units (MPUs) are small discrete particulates, such as pellets, granules, sugar-seeds, minitablets, microparticles, etc., usually smaller than 2 mm in diameter (40-41). Multiparticulate units may be formulated as final dosage forms or subsequently filled into capsules or compressed into tablets. Due to different multiparticulate unit manufacturing methods and composition, the evaluation of their processability is both highly needed and challenging. In order to improve multiparticulate units characterization and provide an in-depth understanding of multiparticulate unit properties, mathematical approaches have been applied (42–50).

The SeDeM Expert System is the most frequently applied mathematical approach for the characterization of multiparticulate units, such as granules and pellets, due to its simple application and the possibility of parameter limits adjustment. Luo et al. (42) applied a modified SeDeM Expert System for microcrystalline cellulose granules, obtained by high shear wet granulation. Granulation was performed in 1, 2 and 4 l vessels and it was found that the radar charts of the obtained granules were similar, indicating a successful process scale-up and granule suitability for direct compression (42). Cui et al. (43) investigated the properties of granules obtained by wet granulation, as the intermediate in ginkgo leaf tablet production, based on the SeDeM Expert System. The expert system-based characterization provided a better understanding of ginkgo granule impact on the ginkgo tablets and aided granule composition and process parameter selection for obtaining optimal tablet properties (43). Khan applied the SeDeM-ODT Expert System for optimization of granules obtained by roller compaction (44). The process variables were selected based on the incidence factors related to granule flowability, compression and disintegration. The SeDeM-ODT Expert System provided information regarding relevant granule properties and predicted compact mechanical properties and disintegration (44).

Hamman et al. (45-46) applied the SeDeM Expert System in order to enhance multiparticulate units compression. They investigated the effects of pellets size (45) and active ingredient incorporated (4) on the multiparticulate compacts, using SeDeM Expert System-based characterization. In the first step, placebo pellets were prepared by extrusion/spheronization in five size ranges (i.e. 0.5, 1.0, 1.5, 2.0 and 2.5 mm) (4). All pellets exhibited *Compression* incidence factors below the acceptable values, irrespective of pellet size. In order to enhance pellet compressibility, directly compressible excipients were added extragranularly, in the amount calculated according to the SeDeM Expert System Equation (1). It was found that copovidone was the most suitable excipient for improving pellet compressibility. The obtained multiparticulate unit compacts exhibited acceptable weight variation, disintegration and mechanical properties, i.e. friability and compact hardness (45), indicating that the SeDeM Expert System provided an excipient

content calculation applicable to multiparticulate units as well. In the subsequent research, Hamman et al. (46) incorporated three different active ingredients, i.e. doxylamine, ibuprofen or paracetamol, and prepared pellets in different size ranges. Copovidone was added to improve multipartiuclate units compressibility. The obtained multiparticulate units compacts exhibited good characteristics in terms of hardness, friability and disintegration time. It was found that three formulations containing ibuprofen and one formulation with paracetamol did not comply to the criteria for content uniformity, described in the European Pharmacopoeia. The dissolution test showed that close to 100% of the model drug was released from the prepared compacts in 2 hours, which was a confirmation of successfully developed and prepared multiparticulate unit compacts, based on the SeDeM Expert System framework (4).

Our research group performed a different multiparticulate units characterization (pellets obtained by extrusion/spheronization, granules obtained by wet granulation, liquisolid pellets, liquisolid powders, 3D printed MPUs) based on the CBCS, MCS and SeDeM Expert System (47–50). Although initially developed for powder characterization, these mathematical approaches provided valuable insight into the attributes of multiparticulate samples affecting their processability. The investigated approaches were applied with certain alterations, in order to improve characterization parameters and relevant parameter limits, e.g. for multiparticulate unit size. Additionally, mathematical transformation was added to the MCS to improve sample characterization and comparison. The results obtained provided insight into multiparticulate material properties and contributed to a mechanistic understanding of the factors governing their processability, and they may serve as a useful tool in multiparticulate dosage forms development (47–50). Mathematical approaches exhibited sufficient discriminatory power to depict the differences among multiparticulate units prepared by different methods, since preparation technology represents the main factor affecting MPU characteristics. However, the differences between MPU composition and the excipients incorporated were not obtained by mathematical approach-based characterization. It may be postulated that these MPU differences exhibit a low impact on further processing and that MPU preparation methods were distinctively reflected by the mathematical approaches applied. Among the listed parameters, flowability and compression-related characteristics should be considered in more detail when further MPU processability is evaluated. The application of mathematical approaches in multiparticulate units characterization represents a promising approach. It may be expanded to provide a guideline, which may be used for knowledge-based final dosage form selection, facilitating multiparticulate-based dosage form development.

Mathematical approach-based online platforms

Knowledge-based formulation development tendencies enforced excipient manufacturers to provide excipient properties relevant for the application of mathematical approaches. Online platforms are being developed and may be applied for formulation development facilitation by interested users.

DFE pharma provides online formulation aid for solid dosage forms development (51). It is available in *Guided* and *Expert* modes, with the following options:

- dosage form selection: immediate release tablet, orodispersible tablet, mini tablet, capsule, sachet;
- manufacturing process selection: direct compression, wet granulation, dry granulation;
- average or median API particle size: small (smaller than 50 μm), medium (50-100 μm), large (larger than 100 μm);
- API concentration in formulation: up to 100%;
- API compactibility: 4 levels, from poor to good;

Based on the input parameters, the formulation tool suggests the excipients and their ratio, alongside additional formulation advice, considerations and mixing order. The application is user-friendly and simple to use (51). However, the API input data is not specific enough and API characteristics are not thoroughly analyzed, which leads to formulation suggestions limited to only a few options. Additionally, the database consists of excipients from the DFE portfolio only, so it was developed as a marketing tool as well.

BASF provides *ZoomLab™-Virtual Formulation Assistant* platform which is more complex in comparison to the DFE pharma software (52). It is also available in two modes, *Beginner* and *Expert*. In the *Beginner* mode, four options are available, including *Formulation Wizard*. It represents a tool for the development of solid dosage forms, based on the following input data:

- dosage form: pellets, tablets
- release kinetics: immediate release or delayed release (enteric-coated dosage forms)
- dosage form target profile: API dose, maximal compaction pressure, preferred tablet weight and tensile strength
- data required for API developability assessment (revised version of Biopharmaceutical Classification System), i.e. API solubility and permeability in gastrointestinal tract assessment

After these steps, the formulation scientist is forewarned about the potential problems, linked with the API physicochemical and biopharmaceutical properties, e.g. particle size distribution, surface area, dissolution rate, solubility, permeability in the small intestine, lipophilicity based on Lipinski's "Rule of Five". Additionally, potential solutions for specific API properties which should be compensated are suggested, and the formulation scientist may revise the input data or formulation goals. Afterwards, the following data input is required:

- API properties: molecular properties (molecular weight, logP, hydrogen bonds, functional groups), bulk properties (true density, D10, D50, D90, angle of repose), compression properties (compaction pressure at zero porosity,

compressibility resistance, tensile strength at zero porosity, bonding capacity), biopharmaceutical properties and API Class within the Biopharmaceutical Classification System, stability challenges (thermal degradation, sensitivity to hydrolysis, light and oxidation),

- preferred excipient type, grades or groups, based on the formulation scientists' experience or excipient availability.

The extensive active ingredients characteristics database is implemented on the platform, so it is possible to perform the formulation development based on the available data, without any need for experimental characterization. After data input, the formulation composition is suggested and the user may modify the suggestions obtained. The current version of the *Formulation Wizard* has been developed for tablet core formulation development. Information regarding tablet coating composition may be provided subsequently, using the additional sections in the platform, *Instant-* and *Enteric-Release Coatings*. In the *Beginner* mode, the *ZoomLab™-Virtual Formulation Assistant* platform is focused on direct compression only, while, in the case of dry granulation or wet granulation, *Expert* mode should be used for the investigated API/powder blend.

Expert mode provides plenty of diverse topics, including *Processability of Active Ingredient* and *Processability of Powder Blend*, tools developed for suitable manufacturing process identification. Powder characterization is based on parameters described in the Pharmacopoeia and Manufacturability Classification System (Table III). The majority of the parameters should be experimentally assessed, while tensile strength values obtained at compression pressure ranges may be extrapolated by the software. After data input, the radar chart and processability interpretation are represented in the platform, similarly to SeDeM Expert System principles. Both API and powder blend characteristics are shown, in order to obtain visual characteristics comparison. Detailed result interpretation and formulation advice is provided, regarding powder processability, particle size, powder density, flowability and tabletability. Potential problems related to each parameter group are emphasized and optimization is performed. It is stated whether each manufacturing process, i.e. direct compression, dry granulation or wet granulation, is applicable for the investigated API/powder blend, which may increase the resource and time invested in the formulation development. Additionally, the API concentration in the blend may be changed and powder blend characteristics may be updated, in order to either incorporate a higher API dose or decrease the API concentration, to perform direct compression. (52).

Table III Parameters and parameter limit values included in the *ZoomLab™-Virtual Formulation Assistant* platform (adapted from reference 52)

Tabela III Parametri i opseg vrednosti parametara opisanih u okviru platforme *ZoomLab™-Virtual Formulation Assistant* (prilagođeno prema referenci 52)

Parameter group	Parameter	Parameter limit value		
		Radius parameter=0	Radius parameter=5	Radius parameter=10
Particle size	D10 value	0	50 μm	100 μm
	D50 value	0	75 μm	150 μm
	D90 value	1700 μm	1000 μm	700 μm
	Distribution span	4.0	3.0	1.0
Density	Bulk density	0	0.5 g/ml	1.0 g/ml
	Tapped density	0	0.5 g/ml	1.0 g/ml
Flowability	Carr index	40%	25%	10%
	Hausner ratio	1.60	1.35	1.10
	Angle of repose	65°	45°	25°
Tabletability	Compaction pressure (at ~0.15 porosity)	2000 MPa	250 MPa	0
	Tensile strength (at ~0.15 porosity)	0	1.0 MPa	8.0 MPa
	Tensile strength at 100 MPa	0	1.0 MPa	8.0 MPa
	Tensile strength at 150 MPa	0	1.5 MPa	12.0 MPa
	Tensile strength at 250 MPa	0	1.5 MPa	12.0 MPa

This platform reflects the potential application of mathematical approaches in both multiparticulate units and tablets formulation development. It represents a major opportunity for facilitating solid dosage form development, due to online availability, implemented API characteristics database and comprehensive analysis of the input data. However, some aspects of the API characterization may be challenging in routine powder assessment in pharmaceutical laboratories, similarly to MCS. Additionally, API and excipient characteristics may vary, so the platform reliability needs to be assessed in the future.

Conclusion

Different mathematical approaches have been developed with the aim of powders and multiparticulate units processability evaluation. The parameters included are based on the powder particulate, bulk and compression-related properties, and different parameters and parameter groups are emphasized within each approach. The application of mathematical approaches for powders and multiparticulate units processability evaluation may contribute to knowledge-based material characterization and may facilitate solid dosage form development and optimization. However, due to the differences among mathematical approaches, the selection of the appropriate one,

providing critical quality attributes assessment, represents a crucial step in their implementation.

Acknowledgment

This work was financially supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (project 451-03-68/2022-14/200161).

References

1. Lionberger RA. FDA critical path initiatives: Opportunities for generic drug development. AAPS Journal. 2008;10:103–9.
2. Leane M, Pitt K, Reynolds G, Anwar J, Charlton S, Crean A, et al. A proposal for a drug product Manufacturing Classification System (MCS) for oral solid dosage forms. Pharm Dev Technol. 2015;20:12–21.
3. Pérez P, Suñé-Negre JM, Miñarro M, Roig M, Fuster R, García-Montoya E, et al. A new expert systems (SeDeM Diagram) for control batch powder formulation and preformulation drug products. Eur J Pharm Biopharm. 2006;64(3):351–9.
4. Sun CC. A classification system for tableting behaviors of binary powder mixtures. Asian J Pharm Sci. 2016;11(4):486–91.
5. Osamura T, Takeuchi Y, Onodera R, Kitamura M, Takahashi Y, Tahara K, et al. Characterization of tableting properties measured with a multi-functional compaction instrument for several pharmaceutical excipients and actual tablet formulations. Int J Pharm. 2016;510(1):195–202.
6. Dai S, Xu B, Zhang Z, Yu J, Wang F, Shi X, Qiao Y. et al. A compression behavior classification system of pharmaceutical powders for accelerating direct compression tablet formulation design. Int J Pharm. 2019;572:118742.
7. Leane, M, Pitt K, Reynolds G. and Manufacturing Classification System (MCS) Working Group. A proposal for a drug product Manufacturing Classification System (MCS) for oral solid dosage forms. Pharm Dev Technol. 2015; 20(1):12-21.
8. Hancock B. Identifying Candidates for Direct Compression Using Material-Sparing Formulation Tools. Paper presented at: AAPS Annual Meeting; 2004 Nov 7-11; Baltimore, USA.
9. McCormick D. Evolutions in Direct Compression. Pharmaceutical Technology. 2005;29(4):52–62.
10. Rohrs BR, Amidon GE, Meury RH, Secreast PJ, King HM, Skoug CJ. et al. Particle size limits to meet USP content uniformity criteria for tablets and capsules. J Pharm Sci. 2006;95:1049–1059.
11. Yalkowsky SH, Bolton S. Particle size and content uniformity. Pharm Res. 1990;7:962–966.

12. Leane M, Pitt K, Reynolds GK, Dawson N, Ziegler I, Szepes A, et al. Manufacturing classification system in the real world: factors influencing manufacturing process choices for filed commercial oral solid dosage formulations, case studies from industry and considerations for continuous processing. Pharm Dev Technol. 2018;23:964–77.
13. Leane M, Pitt K. Adoption of the MCS concept in the pharmaceutical industry. Paper presented at: 12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology; 2021 May 11-14; virtual meeting.
14. Dai S, Xu B, Shi G, Liu J, Zhang Z, Shi X, et al. SeDeM expert system for directly compressed tablet formulation: A review and new perspectives. Powder Technol. 2019;342:517–27.
15. Suñé-Negre JM, Pérez-Lozano P, Miñarro M, Roig M, Fuster R, Hernández C, et al. Application of the SeDeM Diagram and a new mathematical equation in the design of direct compression tablet formulation. Eur J Pharm Biopharm. 2008;69(3):1029–39.
16. Aguilar-Díaz JE, García-Montoya E, Pérez-Lozano P, Suñe-Negre JM, Miñarro M, Ticó JR. The use of the SeDeM Diagram expert system to determine the suitability of diluents-disintegrants for direct compression and their use in formulation of ODT. Eur J Pharm Biopharm. 2009;73(3):414–23.
17. Suñé-Negre JM, Roig M, Fuster R, Hernández C, Ruhí R, García-Montoya E, et al. New classification of directly compressible (DC) excipients in function of the SeDeM Diagarm Expert System. Int J Pharm. 2014;470(1–2):15–27.
18. Scholtz JC, Steenekamp JH, Hamman JH, Tiedt LR. The SeDeM Expert Diagram System: Its performance and predictability in direct compressible formulations containing novel excipients and different types of active ingredients. Powder Technol. 2017;312:222–36.
19. Aguilar-Díaz JE, García-Montoya E, Suñe-Negre JM, Pérez-Lozano P, Miñarro M, Ticó JR. Predicting orally disintegrating tablets formulations of ibuprophen tablets: An application of the new SeDeM-ODT expert system. Eur J Pharm Biopharm. 2012;80(3):638–48.
20. FDA. Guidance for Industry Orally Disintegrating Tablets. 2008.
21. Sipos E, Oltean AR, Szabó ZI, Rédai EM, Nagy GD. Application of SeDeM expert systems in preformulation studies of pediatric ibuprofen ODT tablets. Acta Pharm. 2017;67(2):237–46.
22. Khan A, Majeedullah, Qayum M, Ahmad L, Ahmad Khan S, Abbas M. Optimization of diluents on the basis of SeDeM-ODT expert system for formulation development of ODTs of glimepiride. Adv Powder Technol. 2022;33(2):103389.
23. Rao MRP, Sapate S, Sonawane A. Pharmacotechnical Evaluation by SeDeM Expert System to Develop Orodispersible Tablets. AAPS PharmSciTech. 2022;23(5):1-14.
24. Zieschang L, Klein M, Jung N, Krämer J, Windbergs M. Formulation development of medicated chewing gum tablets by direct compression using the SeDeM-Diagram-Expert-System. Eur J Pharm Biopharm. 2019;144:68–78.
25. Shah DS, Jha DK, Gurram S, Suñé-Pou M, Garcia-Montoya E, Amin PD. A new SeDeM-SLA expert system for screening of solid carriers for the preparation of solidified liquids: A case of citronella oil. Powder Technol. 2021;382:605–18.
26. Mamidi HK, Mishra SM, Rohera BD. Application of modified SeDeM expert diagram system for selection of direct compression excipient for liquisolid formulation of Neusilin® US2. J Drug Deliv Sci Tech. 2021;64:102506.
27. Leuenberger H. The compressibility and compactibility of powder systems. Int J Pharm. 1982;12:41–55.

28. Galdón E, Casas M, Gayango M, Caraballo I. First study of the evolution of the SeDeM expert system parameters based on percolation theory: Monitoring of their critical behavior. Eur J Pharm Biopharm. 2016;109:158–64.
29. Gülbağ S, Yılmaz Usta D, Gültekin HE, Oktay AN, Demirtaş Ö, Karaküçük A, et al. New perspective to develop memantine orally disintegrating tablet formulations: SeDeM expert system. Pharm Dev Technol. 2018;23(5):512–9.
30. Pitt K, Heasley M. Determination of the tensile strength of elongated tablets. Powder Technol. 2013;238:169–75.
31. Pitt KG, Webber RJ, Hill KA, Dey D, Gamlen MJ. Compression prediction accuracy from small scale compaction studies to production presses. Powder Technol. 2015;270(PB):490–3.
32. Nordström J, Klevan I, Alderborn G. A particle rearrangement index based on the kawakita powder compression equation. J Pharm Sci. 2009;98(3):1053–63.
33. Nordström J, Klevan I, Alderborn G. A protocol for the classification of powder compression characteristics. Eur J Pharm Biopharm. 2012;80(1):209–16.
34. Klevan I, Nordström J, Tho I, Alderborn G. A statistical approach to evaluate the potential use of compression parameters for classification of pharmaceutical powder materials. Eur J Pharm Biopharm. 2010;75(3):425–35.
35. Kawakita Kimio, Lüdde Karl-Helmut. Some Considerations on Powder Compresion Equations. Powder Technol. 1971;4(2):61–8.
36. Heckel RW. Density-pressure relationship in powder compaction. Trans Met Soc, AIME. 1961;221:671–5.
37. Ryshkewitch E. Compression strength of porous sintered alumina and zirconia. J Am Ceram Soc. 1953;36:65–8.
38. Duckworth W. Discussion of Ryshkewitch paper. J Am Ceram Soc. 1953;36:68.
39. Worku Z, Kumar D, Gomes J, He Y, Glennon B, Ramisetty K, et al. Modelling and understanding powder flow properties and compactability of selected active pharmaceutical ingredients, excipients and physical mixtures from critical material properties. Int J Pharm. 2017;531(1):191–204.
40. Abdul S, Chandewar AV, Jaiswal SB. A flexible technology for modified-release drugs: Multiple-unit pellet system (MUPS). J Control Release. 2010;147:2–16.
41. Xu M, Heng PWS, Liew CV. Formulation and process strategies to minimize coat damage for compaction of coated pellets in a rotary tablet press: A mechanistic view. Int J Pharm. 2016;499(1–2):29–37.
42. Luo G, Xu B, Zhang Y, Cui X, Li J, Shi X, et al. Scale-up of a high shear wet granulation process using a nucleation regime map approach. Particuology. 2017;31:87–94.
43. Cui XL, Xu B, Zhang Y, Zhang N, Shi XY, Qiao YJ. Application of quality by design in granulation process for ginkgo leaf tablet (I) : comprehensive characterization of granule properties. Zhongguo Zhong yao za zhi = Zhongguo Zhongyao Zazhi = China Journal of Chinese Materia Medica. 2017;42(6):1037–42.
44. Khan A. Optimization of the process variables of roller compaction, on the basis of granules characteristics (flow, mechanical strength, and disintegration behavior): an application of SeDeM-ODT expert system. Drug Dev Ind Pharm. 2019;45(9):1537–46.
45. Hamman H, Hamman J, Wessels A, Scholtz J, Steenekamp JH. Development of multiple-unit pellet system tablets by employing the SeDeM expert diagram system I: pellets with different sizes. Pharm Dev Technol. 2018;23(7):706–14.

46. Hamman H, Hamman J, Wessels A, Scholtz J, Steenekamp J. Development of multiple-unit pellet system tablets by employing the SeDeM expert diagram system II: pellets containing different active pharmaceutical ingredients. Pharm Dev Technol. 2019;24(2):145–56.
47. Vasiljević I, Turković E, Piller M, Zimmer A, Parojčić J. An investigation into applicability of different compression behaviour assessment approaches for multiparticulate units characterization. Powder Technol. 2021;379:526–36.
48. Vasiljević I, Turković E, Nenadović S, Mirković M, Zimmer A, Parojčić J, et al. Investigation into liquisolid system processability based on the SeDeM Expert System approach. Int J Pharm. 2021;605: 120847.
49. Vasiljević I, Turković E, Aleksić I, Parojčić J. An investigation into formulation factor impact on the characteristics of granules prepared by selective laser sintering. Paper presented at: 13th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology; 2022 Mar 28-31; Rotterdam, the Netherlands.
50. Vasiljević I, Turković E, Piller M, Mirković M, Zimmer A, Aleksić I, et al. Processability evaluation of multiparticulate units prepared by selective laser sintering using the SeDeM Expert System approach. Int J Pharm. 2022; 629:122337.
51. DFE pharma [Internet]. Formulation tool; 2022 [cited 2022 Dec 22]. Available from: https://dfepharma.com/formulation-tool/#/en/guided.
52. BASF [Internet]. ZoomLabTM – Virtual Formulation Assistant; 2022 [cited 2022 Dec 22]. https://myapps.basf.com/ZoomLab/Dashboard.

Pregled i kritička analiza matematičkih pristupa za karakterizaciju praškova i višečestičnih sistema u razvoju lekova

Ivana Vasiljević*, Erna Turković, Ivana Aleksić, Jelena Parojčić

Univerzitet u Beogradu – Farmaceutski fakultet, Katedra za farmaceutsku tehnologiju i kozmetologiju, Vojvode Stepe 450, 11221 Beograd, Srbija

*Autor za korespondenciju: Ivana Vasiljević, E-mail: ivanav@pharmacy.bg.ac.rs

Sažetak

Poznavanje uticaja svojstava materijala i procesnih parametara na karakteristike čvrstih farmaceutskih oblika predstavlja osnovu *Quality-by-design* pristupa razvoju lekova. Kako bi bio olakšan razvoj formulacije i izbor proizvodne tehnologije, više istraživačkih grupa opisalo je matematičke pristupe, koji se zasnivaju na čestičnim karakteristikama čestica, osobinama praška i ponašanju materijala pri kompresiji. U ovom radu prikazana su teorijska razmatranja i kritički pregled matematičkih pristupa razvijenih za karakterizaciju praškova i višečestičnih sistema.

Ovi matematički pristupi su, generalno, razvijeni za karakterizaciju materijala pogodnih za direktnu kompresiju. Međutim, u nekim slučajevima se razmatraju i druge tehnologije, kao što su suva i vlažna granulacija. Među opisanim karakteristikama materijala, zatezna čvrstina se izdvaja kao jedna od najznačajnijih za procenu mehaničkih svojstava kompakta. Potrebno je ispitati i protočnost materijala. Takođe, veličina i oblik čestica, gustina materijala i profili koji opisuju kompresibilnost, kompaktibilnost i tabletabilnost materijala prepoznati su kao karakteristike koje značajno utiču na razvoj čvrstih farmaceutskih oblika.

Primena matematičkih pristupa u karakterizaciji praškova i višečestičnih sistema može doprineti mehanističkom razumevanju svojstava materijala i olakšati razvoj i optimizaciju čvrstih farmaceutskih oblika lekova. Međutim, ključno je odabrati odgovarajući pristup, zavisno od željenih karakteristika finalnog preparata, kako bi sva kritična svojstva materijala bila ispitana i kritički razmotrena.

Ključne reči: proizvodnja lekova, čvrsti farmaceutski oblici, zatezna čvrstina, protočnost, klasifikacija materijala