Chapter

SeDeM-ODT Expert System: A Solution to Challenges in Characterization of Pharmaceutical Powders and Powdered Material

Amjad Khan, Shabnam Nazir, Hamad S. Alyami and Aman Ullah

Abstract

In the field of pharmaceutical sciences, material characterization has been a focus of research as properties of the powder ingredients govern characteristics of the finished dosage form. It has been a tedious and time-consuming job to develop a correlation between the characteristics of powder material and final dosage form. Extensive experimentation is carried out at different stages of formulation development to optimize the final blend and produce a product fulfilling official requirements. Various approaches have been applied for the purpose with varying degree of applications. SeDeM-ODT expert system is a novel pre-formulation technique developed for characterization of powder material of varying nature. Experimental and quantitative determination of various parameters provides a basis for SeDeM-ODT expert system. The system predicts suitability of powder material (APIs and excipients) for tablet preparation by direct compression technology and disintegration behavior of the resultant dosage form. It provides a basis for selection of excipients, both quantitatively and qualitatively. The present study covers area of powder characterization at pre-formulation level of pharmaceutical product development. SeDeM-ODT expert system reduces lead time for pre-formulation studies and provides formulations with minimum number of excipients. SeDeM-ODT expert system has been successfully applied for material characterization (APIs and excipients) before processing and after processing.

Keywords: direct compression, powder characterization, pharmaceutical powders, pre-formulation study, SeDeM-ODT expert system

1. Introduction

Tablets are the most preferred dosage form with respect to patient acceptability, flexibility in dose adjustment, easy manufacturing, and better stability [1, 2]. Irrespective of the nature of the drug and its manufacturing technique, tablets should meet some strict requirements in terms of mechanical strength,

disintegration, and drug release [3–5]. A variety of techniques are available for tablet preparation among which direct compression is mostly preferred due to simplicity, cost-effectiveness, and less number of involved steps [6, 7]. However it can be applied only to the powder blend having optimum rheological characteristics, mechanical strength, and disintegration behavior, i.e., the powder blend should flow efficiently, and the resultant tablet should have sufficient mechanical strength with acceptable disintegration behavior [8–10]. All these characteristics are interlinked, and usually improvement of one characteristic can adversely affect the other. Hit and trial is the mostly applied method for optimization of powder characteristics which is laborious and material consuming. Optimization of powder blend is carried out, mostly, in the last stage of formulation development (following pre-formulation studies). Usual reported time for formulation development is in the range of 14–20 days, which can further extend in certain cases. There was a need for a technique that can avoid the experimentation for optimization of powder characteristics and help in excipient selection, i.e., select proper quantity of an excipient with desired characteristics. SeDeM-ODT expert system is a pre-formulation tool and has solved most of the problems associated with material characterization at pre-formulation level. SeDeM-ODT expert system minimizes experimentation and facilitates the process of formulation development by helping in excipient selection (in terms of desired characteristics and required quantity).

2. SeDeM-ODT expert system

SeDeM-ODT expert system is novel pre-formulation technique applied for development of a solid dosage form (tablets) by direct compression technology [11]. The system characterizes powder substance on the basis of various parameters related to flow, compressibility, and disintegration behavior. Physical profile of powder substance is developed, suggesting its suitability for direct compression and bucco-dispersibility [12, 13]. SeDeM expert system can be segmented into the following:

SeDeM expert system: It determines suitability of the powder substance for direct compression only [11, 13]. That is, the system characterizes powder substance with respect to its rheological characteristics and compressibility.

SeDeM-ODT expert system: It is the newest version of SeDeM expert system and characterizes the powder substances with respect to rheological characteristics, compressibility, and disintegration behavior, simultaneously [14]. Three extra parameters related to characterization of disintegration behavior are included in the SeDeM-ODT expert system.

The SeDeM-ODT expert system has been introduced with the aim of designing oro-dispersible tablets (ODTs) by direct compression [14]. This system is unique as it provides an oro-dispersible tablet formulation by direct compression, i.e., it links prediction of suitability of powder for direct compression and rapid disintegration of the tablets. SeDeM-ODT expert system is used for evaluation of critical quality attributes of powder substance, having an impact on the final product. Quality by Design guidelines ICH-Q8 [15] provides the basis for SeDeM-ODT expert system.

SeDeM-ODT expert system also calculates the amount of excipients with certain characteristic required for the correction of a particular property in order to make a final blend suitable for direct compression [14]. Several parameters have been selected that must be fulfilled by the formulation (excipients) to ensure successful and robust processing by direct compression technology.

2.1 Parameters determined for characterization of powder material

On the basis of physical characteristics and functionality of the ingredients, various parameters are grouped into six factors, as follows:

2.1.1 Dimension factor

Parameters included in this factor affect the size of the tablet and its ability to pile up. Results of these parameters are also used in the mathematical calculation of other indices related to powder compressibility. Parameters included in this group are:

- Bulk density
- Tapped density

2.1.2 Compressibility factor

The factor comprised of the parameters related to compressibility of powder and includes the following:

- Inter-particle porosity
- Carr's index
- Cohesion index

2.1.3 Flow ability/powder flow factor

This factor governs flow ability of the powder during compression and includes the following:

- Hausner ratio
- Angle of repose
- Flow ability

2.1.4 Lubricity/stability factor

Lubricity during compression and stability of the compressed tablets are affected by the parameters included in this factor. These are the following:

- Loss on drying
- Hygroscopicity

This incidence factor shows the rheological properties and stability of the powder and depends upon the intrinsic moisture and hygroscopicity of the material [14]. The low value of this incidence factor shows that the product will absorb moisture from the atmosphere, worsening its rheological properties (flow and compression) and consequently altering product stability. In case of values below the acceptable limit, the following measures are taken:

- Drying of material to reduce its loss on drying.
- Product should be processed in a controlled environment at low humidity.

2.1.5 Lubricity/dosage factor

Parameters included in this factor affect the lubricity and dosage of the tablet and comprised of the following:

- Particles having size below 50 μm
- Homogeneity index

2.1.6 Disgregability

Parameters included in disgregability factor govern disintegration behavior of the final product and are specified for fast dispersible tablets. Parameters included in this factor are as follows:

- Effervescence test
- Disintegration time with disk
- Disintegration time without disk

Incidence factor	Parameter	Symbol	Unit	Equation	Limits	Applied factor
Dimension	Bulk density	Da	g/mL	Da = P/Va	0–1	10 V
	Tapped density	Dc	g/mL	Dc = P/Vc	0–1	10 V
Compressibility	Inter-particle porosity	Ie	—	Dc – Da/Dc × Da	0–1.2	10 V/1.2
	Carr's index	Ic	%	100 (Dc–Da)/ Dc	0–50	V/5
	Cohesion index	Icd	N	*Experimental	0–200	V/20
Flow ability/powder flow	Hausner ratio	IH	—	Dc/Da	3–1	(30–10 V)/2
	Angle of repose	(α)	o	$\tan^{-1}$ (h/r)	0–50	10 – (V/5)
	Powder flow	t″	S	Experimental	0–20	10 – (V/2)
Lubricity/stability	Loss on drying	%HR	%	Experimental	0–10	10 – V
	Hygroscopicity	%H	%	Experimental	0–20	10 – (V/2)
Lubricity/dosage	Particles <50	%Pf	%	Experimental	0–50	10 – (V/5)
	Homogeneity index	IΘ	—	*Fm/100 + ΔFmn*	0–2 × 10^{-2}	500 V
Disgregability	Effervescence time	DE	Min	Experimental	0–5	(5 – V) × 2
	D. time with disk	DCD	Min	Experimental	0–3	(3 – V) × 3.333
	D. time without disk	DSD	Min	Experimental	0–3	(3 – V) × 3.333

D. time with disk: Disintegration time with disk.
D. time without disk: Disintegration time without disk.
**Experimental; The parameter was determined experimentally.*

Table 1.
Basic parameters of SeDeM-ODT expert system divided into different incidence factors.

Table 1 shows the basic parameters determined according to the SeDeM-ODT expert system along with their symbols, units, and classification into different incidence factors.

3. Methodology for powder characterization by SeDeM-ODT expert system

To determine the suitability of powder/powder blend for direct compression and bucco-dispersibility, SeDeM-ODT expert system needs 15 parameters to be found out. The individual parameters of SeDeM-ODT expert system are determined according to their respective pharmacopoeial methods, reported methods, or calculation on the basis of other basic parameters.

Characterization of powder according to the SeDeM-ODT expert system [11, 14] involves the following:

- Determination/calculation of basic parameters
- Conversion of experimental values to "r" values by applying specific factors and graphical presentation of results
- Calculation of various indices on the basis of "r" values

3.1 Determination/calculation of basic parameters of SeDeM-ODT expert system

SeDeM-ODT expert system is based on 15 basic parameters [14] which are determined experimentally or calculated on the basis of other included parameters. Procedures for the determination of basic parameters are given below:

3.1.1 Bulk density

Bulk density of the powder substance is determined according to the USP using graduated cylinder method [16]. The volume of the weighed amount of powder is determined using a graduated cylinder, and the density is calculated using the following equation:

$$D = \frac{m}{V} \tag{1}$$

where D is the density of the powder (g/mL), m is the weight of the powder (g), and v is the volume of the powder (mL).

3.1.2 Tapped density

Tapped density of powdered material is determined according to the USP by tapping known volume of powder taken in a graduated cylinder and noting the volume reduction [16]. Tapping can be carried out manually or using mechanical tappers.

3.1.3 Inter-particle porosity

Values of bulk density and tapped density are used for the calculation of inter-particle porosity [17], using the following equation:

$$\text{Ie} = \frac{\text{Dc} - \text{Da}}{\text{Dc x Da}} \tag{2}$$

where Ie is the inter-particle porosity, Dc is the tapped density (g/mL), and Da is the bulk density (g/mL).

3.1.4 Carr's index

Carr's index is calculated on the basis of tapped density and bulk density of powder [16]:

$$\text{C.I.} = \frac{\text{Dc} - \text{Da}}{\text{Dc}} \text{ x } 100 \tag{3}$$

where C.I. is the Carr's index of the powder (%), Dc is the tapped density of the powder (g/mL), and Da is the bulk density of the powder (g/mL).

3.1.5 Cohesion index

Cohesion index is the crushing strength of powder compressed, preferably in an eccentric press under maximum pressure without capping and lamination [11]. The mean crushing strength is calculated for at least 10 compacts, indicating the cohesion index of the powder. The raw powder is tested for compressibility, and in case of failure, 3.5% of the following mixture is added to the mix:

- Talc 2.36%
- Aerosil® 200 0.14%
- Magnesium stearate 1.00%

3.1.6 Hausner ratio

Hausner ratio is calculated from bulk density and tapped density of powder [16] according the equation given below:

$$\text{Hr} = \frac{\text{Dc}}{\text{Da}} \tag{4}$$

where Hr is the Hausner ratio of the powder, Dc is the tapped density of the powder (g/mL), and Da is the bulk density of the powder (g/mL).

3.1.7 Angle of repose

Angle of repose is determined by funnel method [18]. The test powder is allowed to flow from a glass funnel fitted at certain height, and angle of repose was determined using the equation:

$$\propto = \tan^{-1}\left(\frac{H}{r}\right) \quad (5)$$

where α is the angle of repose of powder (°), H is the height of the cone formed by powder (cm), and r is the radius of the base of cone formed by powder (cm).

3.1.8 Powder flow

Powder flow is determined, in accordance with the European Pharmacopeia, by measuring the time required for the powder (100 g) to flow through the orifice of a glass funnel fitted at certain height [19].

3.1.9 Loss on drying

Loss on drying is determined gravimetrically according to the USP [20], using a halogen moisture analyzer. The powder (1 g) is loaded into the pan of moisture analyzer and heated for specified time at 100°C, and the value of percent loss is noted.

3.1.10 Hygroscopicity

Hygroscopicity is measured by placing the accurately weighed amount of powder in a climatic chamber at 75 ± 5% relative humidity for 24 h at ambient temperature. The material is analyzed after 24 h for percent weight gain by reweighing [13], indicating its hygroscopicity.

3.1.11 Particle size distribution

Sieve shaker fitted with standard sieves of pore size 850, 600, 425, 300, and 250 μm is used for the determination of particle size distribution. The powder (100 g) is loaded on the top sieve and the sieve shaker is vibrated for 10 min. The percent amount of the powder retained over each mesh is calculated [21].

3.1.12 Homogeneity index

Homogeneity index is determined according to the European Pharmacopoeia [21]. The powder (100 g) is loaded to a sieve shaker fitted with sieves of 850, 500, 425, 300, 250, and 50 μm pore size, and the sieve shaker is vibrated for 10 min. The percent amount of powder retained over each sieve and that passed through a 50 μm sieve is calculated. Homogeneity index of the material is calculated using the equation mentioned below:

$$I\theta = \frac{Fm}{100 + \Delta Fmn} \quad (6)$$

where Iθ is the relative homogeneity index and Fm is the percentage of particles in the majority range.

If the percentage is higher than that calculated in the complete sieve test, it is because some of the particles become adhered to the product retained in the sieves during the grain size test, and the percentage of particles below 50 μm particles found may be lower than the true figure. The following equation (Eq. (7)) is then applied to the data obtained.

$$I\theta = Fm/100 + (dm - dm - 1)\,Fm - 1 + (dm + 1 - dm)\,Fm + 1 + (dm - dm - dm - 2)\,Fm - 2 + (dm + 2 - dm)\,Fm + 2 + \ldots + (dm - dm - dm - n)\,Fm - n + (dm + n - dm)\,Fm + n \quad (7)$$

where Iθ is the relative homogeneity index and particle size homogeneity in the range of the fractions studied; Fm is the percentage of particles in the majority range; Fm − 1 is the percentage of particles in the range immediately below the majority range; Fm + 1 is the percentage of particles in the range immediately above the majority range; n is the order number of the fraction studied under a series, with respect to the major fraction; dm is the diameter of the particles in the major fraction; dm − 1 is the mean diameter of the particles in the fraction of the range immediately below the majority range; and dm + 1 is the mean diameter of the particles in the fraction of the range immediately above the majority range.

The major fraction (Fm) corresponds to the interval from 0.100 to 0.212 mm, because it falls in the middle of the other fractions of the table. This interval is calculated as the proportion in which the powder particles are found in each fraction considered in the table (as described above). Those particles located in the major fraction (Fm) in a proportion of 60% are considered to represent the minimum acceptable value of 5. The distributions of the other particles are considered to be Gaussian. The limits for the homogeneity index are set between 0 and 0.02.

3.1.13 Effervescence time

Effervescence test for powder compact is determined as per official monograph [22]. The powder is compressed into tablets under maximum pressure without any capping and lamination. One tablet is placed in a beaker containing 200 mL of purified water at ambient temperature. Time taken by the tablet to disperse completely is taken as its effervescence time. Tablet is said to be dispersed completely when there is no agglomerate of the particles. In the context of SeDeM expert system, effervescence does not mean conventional acid-base reaction rather refers to dispersion of the compact in water. Effervescence time is an indicator for oro-dispersible tablets. When tablet disaggregates in less than 5 min, it is considered suitable for oral disintegration.

3.1.14 Disintegration time with disk

The powder is compressed under maximum pressure without any capping or lamination and subjected to the determination of disintegration time using USP disintegration apparatus. Disintegration time with disk is determined for at least six tablets, using de-ionized water as a medium held at 37 ± 2°C [23], and their mean is calculated (n = 6).

3.1.15 Disintegration time without disk

Disintegration time is determined as described in the previous section without any disk [23].

All the basic parameters of SeDeM-ODT expert system, along with symbols, units, and acceptable limits, are listed in **Table 1**.

3.2 Conversion of experimental values (V) to radius values (r) and graphical presentation of results

Results of SeDeM-ODT expert system are graphically presented as SeDeM-ODT diagram built on the basis of basic parameters. Values obtained from the

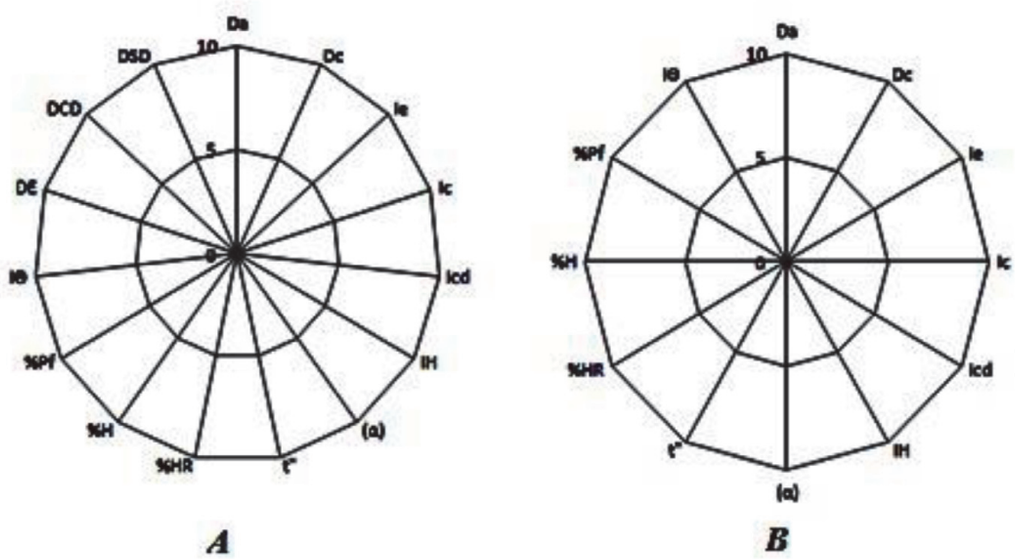

Figure 1.
Diagrammatic presentation of (A) SeDeM-ODT and (B) SeDeM expert system. Da, bulk density; %HR, loss on drying; dc, tapped density; %H, hygroscopicity; Ie, inter-particle porosity; %Pf, particle size; IC, Carr's index; Iθ, homogeneity index; ICd, cohesion index; DE, effervescence test; IH, Hausner ratio; DCD, disintegration time with disk; A, angle of repose; DSD, disintegration time without disk; t , flow ability.

experimental determination or calculations of various parameters are converted to "r" values by applying specific factors, representing radii of the diagram. The diagram is formed by connecting radius values with linear segment [13], having 0 as a minimum value, 10 as maximum value, and 5 as minimum acceptable value as shown in **Figure 1**. The resultant diagram indicates suitability of the material to be compressed by direct compression.

3.3 Calculation of various indices

Optimum mechanical strength, disintegration behavior, and rheological characteristics of powder are estimated on the basis of the following indices [11, 14] calculated using "r" values of the basic parameters.

3.3.1 Parametric index

Parametric index is the ratio of number of parameters having "r" values equal to or greater than 5 to the total number of parameters determined during the study. Parametric index was calculated using the following equation:

$$\text{I.P} = \frac{\text{No.P} \geq 5}{\text{No.Pt}} \tag{8}$$

where I.P. is the parametric index, No. P ≥ 5 is the number of parameters with "r" values equal to or more than 5, and No. Pt is the total number of parameters determined.

Acceptability limit corresponds to a score of 5.

3.3.2 Parameter profile index

Parameter profile index is the average of "r" values of all the parameters determined in the study, and its acceptable limit corresponds to a score of 5.

IPP = Average of "r" value of all parameters

3.3.3 Good compressibility and bucco-dispersibility index

Good compressibility and bucco-dispersibility index (IGCB) is the product of parameter profile index and reliability factor:

$$\text{I.G.C.B} = \text{I.P.P} \times f \tag{9}$$

where f is the reliability factor.

Inclusion of more parameters in the study will increase reliability factor. Its values are as follows:

- For infinite number of parameters, $f = 1$ (maximum value)
- For 15 parameters, $f = 0.971$
- For 12 parameters, $f = 0.952$
- For 08 parameters, $f = 0.900$

3.4 Determination of acceptable limit values for each parameter of SeDeM-ODT expert system

Certain limit values are set for each parameter included in SeDeM-ODT expert system on the basis of experimental results and values described in the *Handbook of Pharmaceutical Excipients* [24]. The rationale for establishing limit values for each parameter is given below.

Limit values of bulk density, tapped density, inter-particle porosity, and Carr's index are calculated from the extreme values of these parameters given in the *Handbook of Pharmaceutical Excipients* and official monograph.

Limit of Icd is obtained by compressing powder into tablet under maximum compression force to get tablets without capping. Maximum hardness at which tablets are compressed without any capping is taken as upper limit, while 0 is taken as lower limit. 0 shows that powder cannot be compressed into tablet.

Limits for angle of repose, IH, and powder flow were set as per official monograph. **Table 2** shows correlation of flow characteristics of powder to various rheological parameters on the basis of the USP [20].

Limits for hygroscopicity are based upon the *Handbook of Pharmaceutical Excipients* [24]. As per published literature [25–27], rheological and compression

Flow characteristics	Carr's index	Hausner ratio	Angle of repose
Excellent	≤10	1.00–1.11	25–30
Good	11–15	1.12–1.18	31–35
Fair—aid not needed	16–20	1.19–1.25	36–40
Passable—may hang up	21–25	1.26–1.34	41–45
Poor—must agitate, vibrate	26–31	1.35–1.45	46–55
Very poor	32–37	1.46–1.59	56–65
Very very poor	>38	>1.6	>66

Table 2.
Relationship between flow characteristics and various rheological parameters.

Sieve size (mm)	Fraction	Average diameter of particles of fraction	Corresponding diameter (dm ... dm ± n)	Difference of dm with major fraction
0.355–0.500	Fm + 2	427	dm + 2	271
0.212–0.355	Fm + 1	283	dm + 1	127
0.100–0.212	Fm	156	dm	0
0.050–0.100	Fm −1	75	dm −1	81
<0.050	Fm −2	25	dm −2	131

Table 3.
Particle size distribution for the determination of homogeneity index.

problems are encountered when the ratio of the fine particles exceeds 25% of the formulation.

Size distribution of the particles provided a basis for assigning limit values to homogeneity index. **Table 3** indicates the size of the sieve (in mm), average particle size in each fraction, the difference in average particle size in the fraction between 0.100 and 0.212, and others.

As the sieve range 0.100–0.212 mm falls in the middle of other factions, it corresponds to major fraction. A proportion of 60% in major fraction (Fm) is considered to be the minimum acceptable value, that is, 5. Distribution of particles into other fractions is considered to be Gaussian. Limit of homogeneity index is 0–0.02.

Initially, relative humidity was calculated based on the establishment of three intervals because the percentage relation obtained from the measurement of the humidity of the substance does not follow a linear relation with respect to the correct behavior of the dust. Humidity below 1% makes the powder too dry, and electrostatic charge is induced, which affects the rheology. Furthermore, low humidity percentages do not allow compression of the substance (moisture is necessary for compacting powders). Moreover, more than 3% moisture causes caking, in addition to favoring the adhesion to punches and dyes. Consequently, it was considered that this parameter should present optimal experimental values from 1 to 3%. Nevertheless, experience using the SeDeM diagram has demonstrated no significant variations in the results, so the previous three intervals of relative humidity can be simplified to the calculation of the parameter; thus, finally, the linear criterion of treatment of results is adopted.

4. Practical applications of SeDeM-ODT expert system

The SeDeM/SeDeM-ODT expert system is based on the experimental study and quantitative determination of the characterization parameters of powdered substances, with the aim to determine suitability for producing tablets by direct compression technology. Additionally, this expert system also provides formulations with a minimum number of excipients and reduces the lead time during formulation development [11]. Some of the reported applications of SeDeM-ODT expert system are summarized below:

4.1 Formulation development by direct compression technology

Direct compression is the most preferred technique for tablet manufacturing due to simplicity, material safety, and cost-effectiveness. Direct compression technique cannot be applied for every formulation because of some strict requirements

in terms rheological characteristics and compressibility [2, 3]. Intensive experimentation is carried out to get a final powder blend suitable for direct compression. SeDeM-ODT expert system has been applied for characterization of powder to predict its suitability for direct compression. The main advantage of the expert system is to avoid extra experimentation during formulation development, reducing time and cost of formulation development [11]. Various mathematical equations are used for powder characterization, and a data base is developed which facilitates the selection of excipients having desired characteristics, at pre-formulation level.

Johny et al. applied SeDeM expert system in formulation development of orodispersible tablets of ibuprofen by direct compression [11]. They developed formulation after characterization of API (ibuprofen) and 21 disintegrants. Various parameters were determined for all the 21 disintegrants, according to the standard protocols, converted to "r" values by applying specific factors, and presented as SeDeM diagram (**Figure 2**). Deficiencies were found out for each disintegrant and were solved by proper selection of other excipients.

In another study SeDeM expert system was applied for formulation development of effervescent tablets of domperidone by direct compression [28]. During the study SeDeM profile was developed for domperidone, effervescent pair (citric acid, tartaric acid, and sodium bicarbonate), and two diluents (Tablettose-80 and

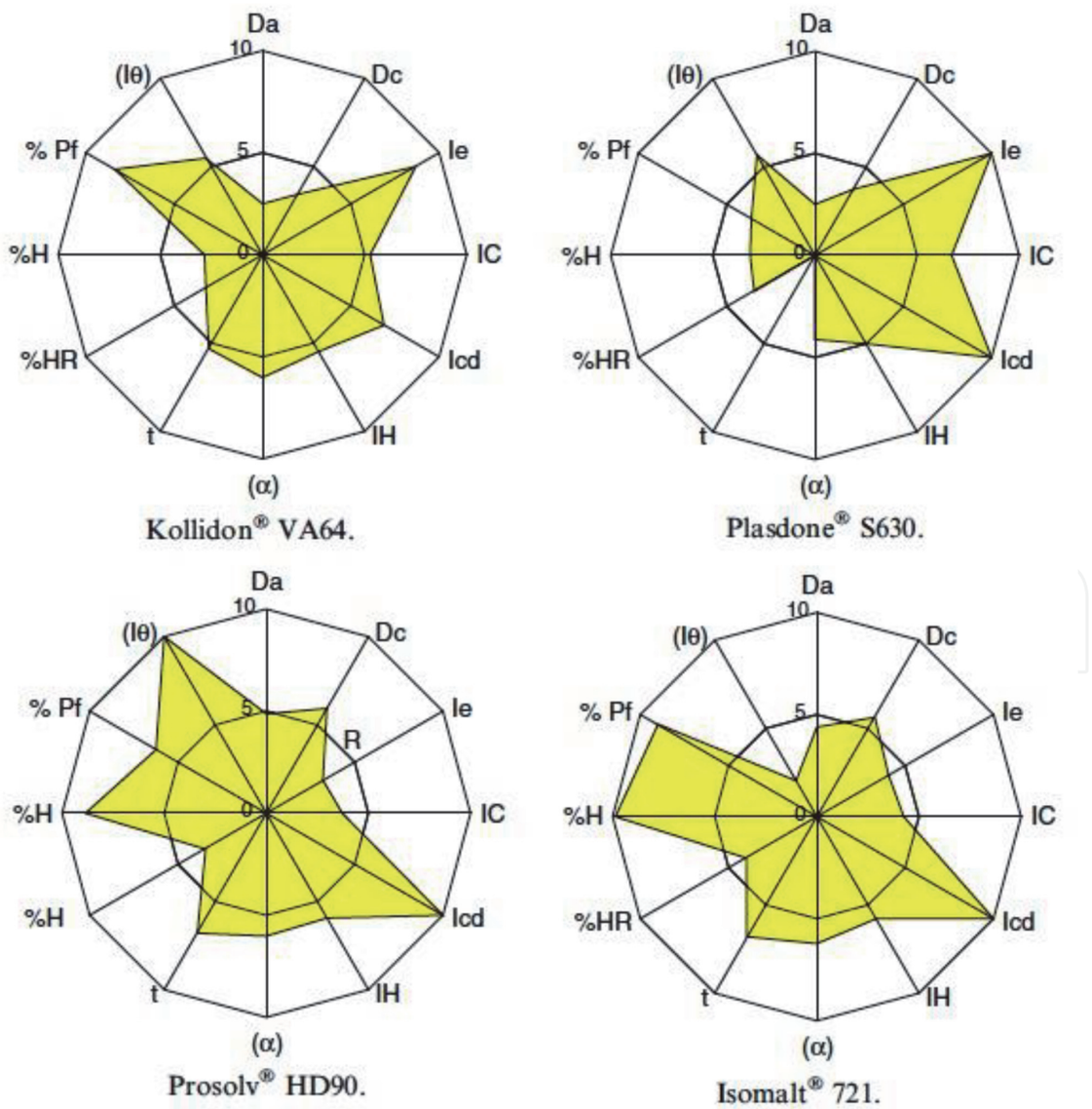

Figure 2.
SeDeM diagram of various disintegrants [11].

microcrystalline cellulose). The model drug, domperidone, was characterized, according to the established procedure, and was found deficient in dimension, compressibility, and flowability/powder flow factors. Index of good compressibility (IGC) value of domperidone was below the acceptable limit. Combination of diluents was used to get a diluent system (**Figure 3**) capable of compensating lower IGC value of domperidone. The developed formulations resulted in tablets fulfilling the official requirements without any stability issue with minimum experimental work.

In a study SeDeM expert system was applied for establishing a design space and determination of critical quality attributes during formulation development of captopril SR matrix by direct compression [29].

Cefuroxime axetil and paracetamol have poor rheological characteristics and compressibility. Inderbir and Pradeep [30] applied the SeDeM expert system for formulation of these two APIs by direct compression. Both the APIs were characterized following standard procedure, and excipients were selected on the basis of mathematical calculations [14].

4.2 Determination of the amount of excipient required for the compression of an API

Josep et al. developed a mathematical Equation [14] for the calculation of the amount of diluent required for the preparation of tablets by direct compression containing glucosamine salt (750 mg). Glucosamine is used in high dose (750 mg/tablet) and presents poor rheological characteristics and compressibility. Six direct compression diluents were characterized according to the SeDeM expert system, and mathematical equation was applied for the calculation of the amount of excipient to compensate the deficiencies. The theoretical model was validated by studying the calculated amounts experimentally.

$$CP = 100 - \left(\frac{RE - R}{RE - RP}\right) \times 100) \tag{10}$$

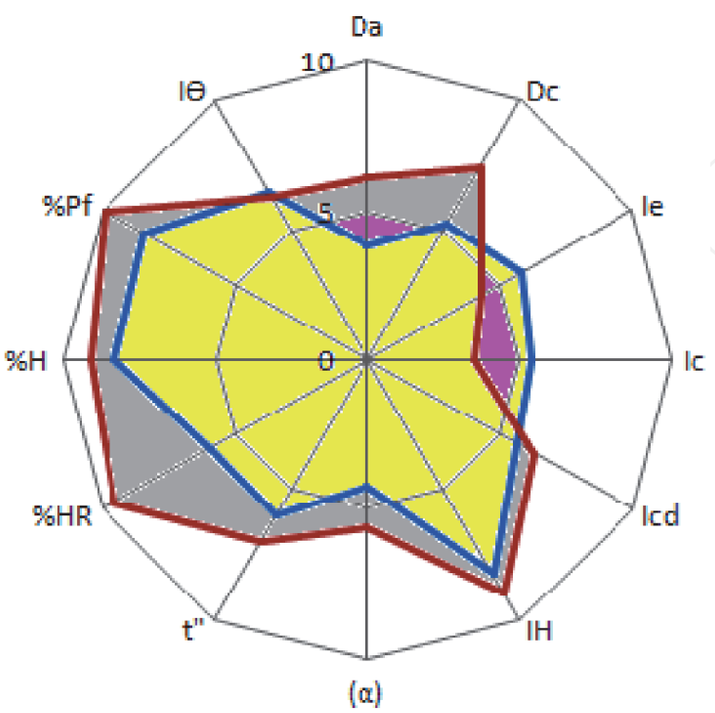

Figure 3.
SeDeM diagram of microcrystalline cellulose and Tablettose-80 [28].

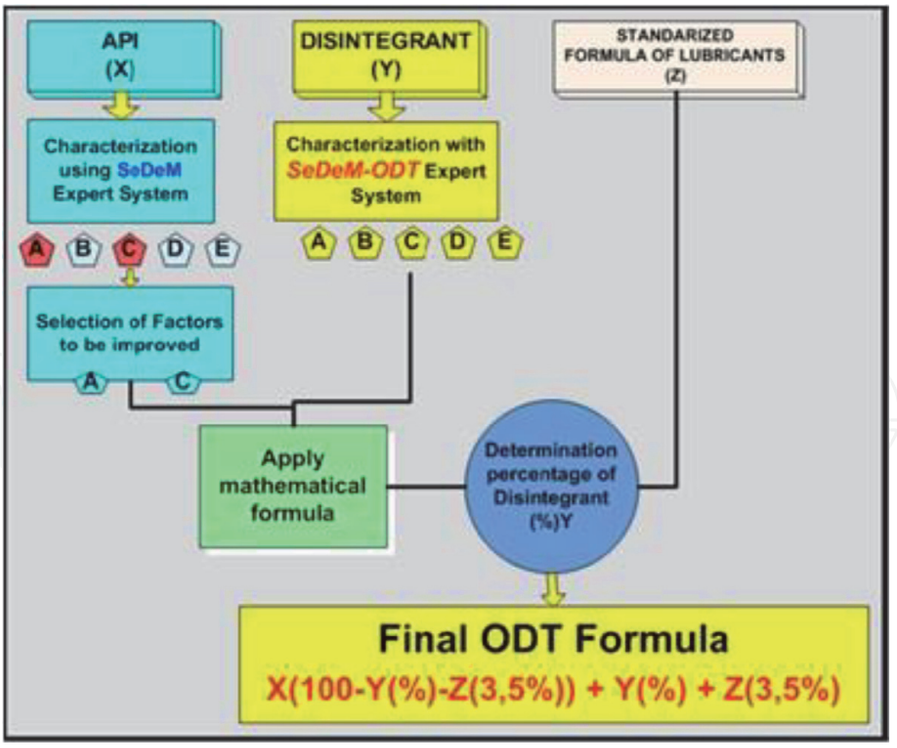

Figure 4.
Strategy proposed by SeDeM expert system to develop orally disintegrating tables [14].

where CP is the % of corrective excipient, RE is the mean-incidence radius value (compressibility) of the corrective excipient, R is the mean-incidence radius value to be obtained in the blend, RP is the mean-incidence radius value (compressibility) of the API to be corrected, and R is the 5 as 5 is the minimum value that is regarded as necessary in order to achieve good compression [14].

Figure 4 presents a strategy for the development of orally disintegrating tablets by direct compression by applying the proposed equation (Eq. (10)).

4.3 Elucidation of the effect of processing on characteristics of powder substances

SeDeM-ODT expert system has been applied for elucidation of the effect of processing parameters on characteristics of powder substance. Amjad et al. applied SeDeM-ODT expert system for predicting the effect of taste masking on the rheological characteristics, mechanical strength, and disintegration behavior of highly water-soluble drug (Itopride HCl) [31]. Itopride HCl is a bitter-tasting, highly water-soluble drug with poor rheological characteristics. Taste of Itopride HCl was masked by water-based wet granulation technique using HPMC as taste masking polymer. Itopride HCl powder was the subjected characterization as per SeDeM-ODT expert system, before and after taste masking, and results were compared (**Figure 5**) to evaluate the effect on rheological characteristics, disintegration behavior, and mechanical strength. Dimension factor and flowability/powder flow factors were below the acceptable limit. Comparison of results before and after taste masking showed that taste masking significantly improved the mechanical strength and rheological characteristics and decreased the disintegration behavior of powder. It was concluded that in order to formulate by direct compression, the formulation will require large amount of disintegrant to overcome increase in mechanical strength after taste masking.

Amjad [32] has applied SeDeM-ODT expert system for the optimization of process variables of roller compaction. He studied ribavirin powder and powder

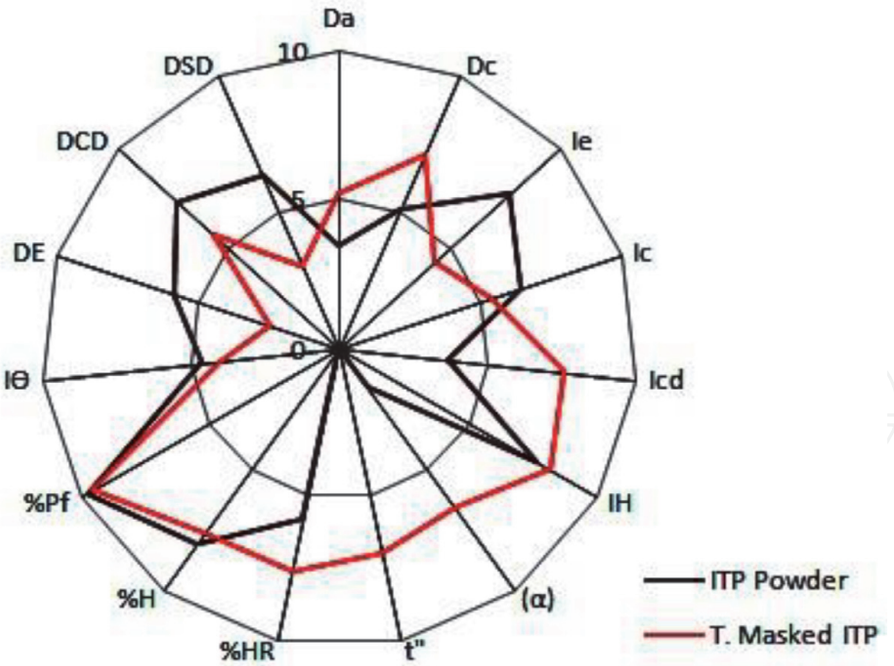

Figure 5.
SeDeM-ODT diagram for Itopride HCl before and after taste masking [33].

blend containing ribavirin and other ingredients included in granule formulation. Powder blend was compacted under varying degree of experimental conditions, and selected in the optimal conditions with better granule characteristics. He claimed that it decreased experimental work and resulted in granules suitable for compression and encapsulation.

4.4 Prediction of behavior of a new pharmaceutical ingredient (APIs and excipients)

SeDeM-ODT expert system has been applied for the determination of suitability of new powdered substances for direct compression. The powder substance may be a new API or excipients which are intended to be used in formulation of compact solid dosage forms.

Sune-Negre et al. used the SeDeM method to characterize an active product ingredient in powder form (API SX-325) and to determine whether it is suitable for direct compression [12], applying the profile to the SeDeM diagram. Twelve parameters were determined for the powdered raw material according to the standard protocols, presented as SeDeM diagram, indicating suitability of the material for direct compression. Findings of the study implied deficient rheological characteristics and poor stability. The product was declared hygroscopic on the basis of SeDeM profile and tended to capture moisture, worsening rheological characteristics and impairing its stability. Various precautionary measures were suggested for prevention of negative effects like drying of the material and tablet preparation in an environment of controlled humidity (relative humidity below 25%).

Sune-Negre et al. applied SeDeM expert system for characterization of 51 directly compressible excipients [12]. On the basis of the results, directly compressible excipients were classified into different groups with different rheological and compressibility capability, and a periodic table of directly compressible excipients was developed, as shown in **Figure 6**.

They showed that the best excipient for direct compression should have an index of good compressibility of 8.832 [12]. SeDeM expert system has been applied for the

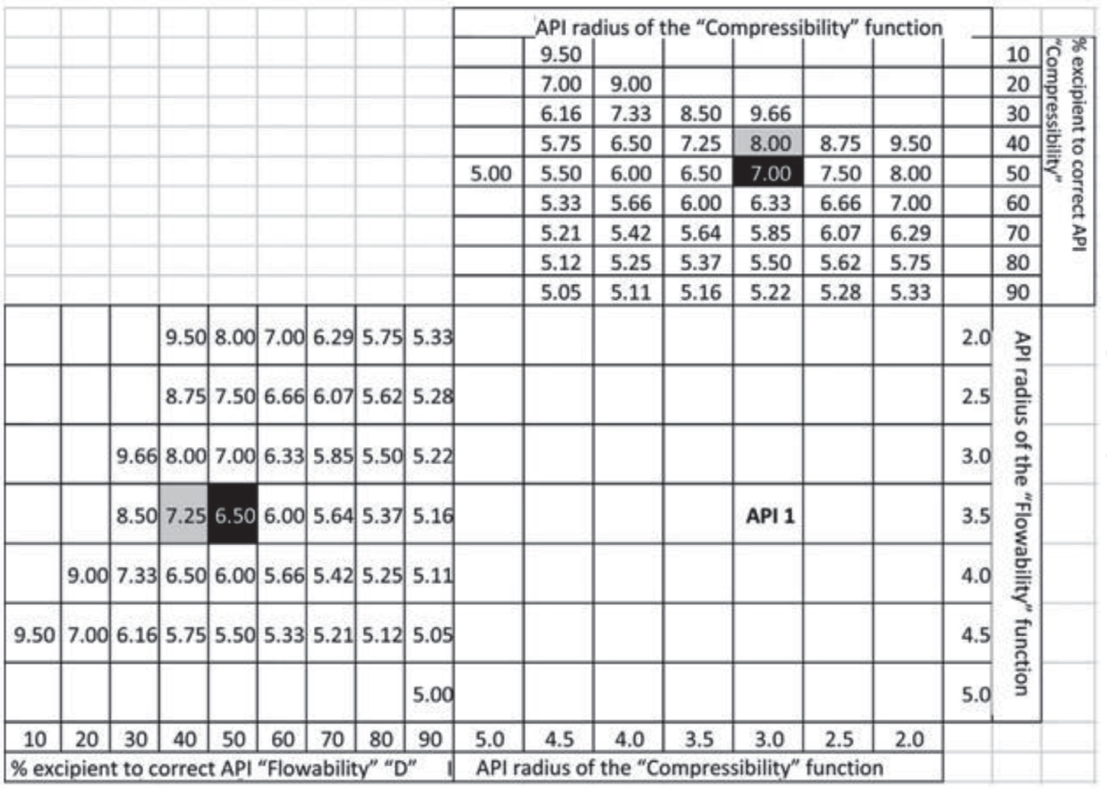

Figure 6.
Correction of "compressibility" and "flowability" of APIs with excipient [12].

determination of reproducibility of various batches of pharmaceutical ingredients (APIs and excipients). Various batches were characterized according to the SeDeM expert system, and reproducibility was estimated on the basis of consistency of the results [13].

4.5 Optimization of powder characteristics

Josep et al. [33] applied SeDeM expert system for the optimization of Hausner ratio and relative humidity. The proposed optimization did not involve any conceptual change in the parameters considered or did a significant change in the results obtained compared with the previous calculation methodology initially established, meaning that the conclusion obtained by applying this method is equivalent [33].

4.6 Quality control of batches of pharmaceutical powders (APIs and excipients) prepared by the same procedure

SeDeM expert system can be applied for the determination of reproducibility of manufacturing process of pharmaceutical powder substance (API and excipients). By establishing specifications for different parameters as per SeDeM-ODT expert system, variation among different batches of a product produced by the same manufacturing process can be determined [34]. **Figure 7** shows the SeDeM diagram of different batches of glucosamine sulfate, prepared by the same manufacturing procedure.

4.7 Differentiation of excipients with same functionality

SeDeM-ODT expert system has been applied for the differentiation of excipients having the same chemical nature and function on the basis of physical

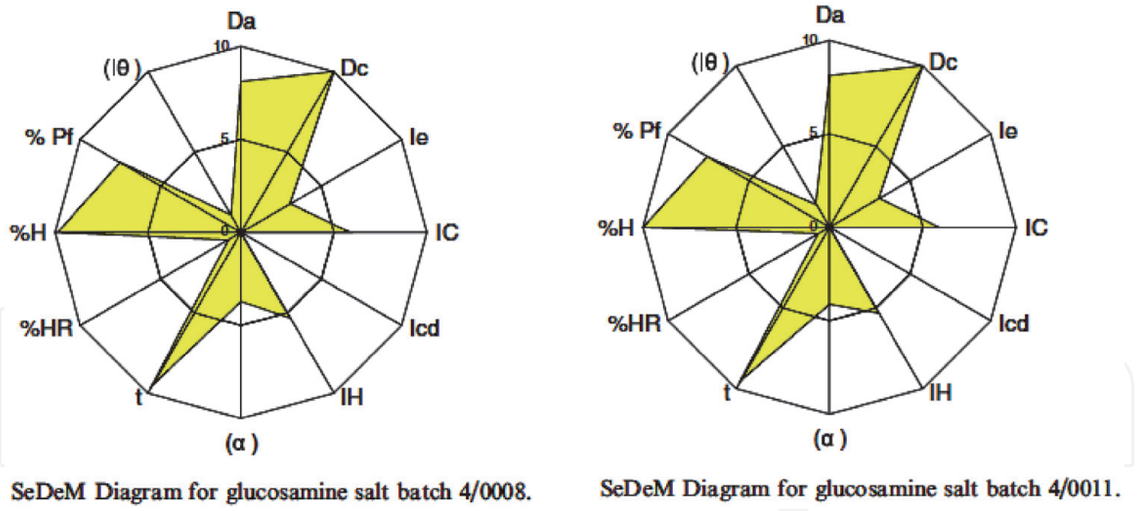

Figure 7.
SeDeM diagram of different batches of glucosamine sulfate [35].

characteristics [35]. For example, various disintegrants and diluents were characterized on the basis of the expert system [13], and the suitable one is selected for a particular formulation. Various parameters are determined according to the SeDeM expert system, deficiencies are defined, and an adequate substance can be selected to get a final blend suitable for direct compression. In a study [11] several lactose were characterized and differentiated on the basis of SeDeM expert system.

5. Conclusions

SeDeM-ODT expert system is a novel tool for the characterization of powder substances on the basis of their physical parameters. The system has been successfully applied for the determination of rheological characteristics, mechanical strength, and disintegration behavior of pharmaceutical powders (APIs and excipients) and determination of suitability for direct compression and buccodispersibility. SeDeM-ODT expert system facilitates the process of excipient selection and calculation of their relative proportion in oral solid dosage form. A data base can be developed for various excipients which will help in the selection of excipients having desired characteristics. It avoids extra experimentation for optimization of various characteristics of powder blend, reducing the cost and time span of formulation development process. This method characterizes the individual components of a formulation and applies a mathematical analysis to determine the exact amount of each ingredient in the final formulation. This innovative tool is consistent with the current requirements of regulatory health authorities such as the FDA and ICH, whereas data generated on the basis of the system can contribute to the concept of Quality by Design. SeDeM-ODT expert system has certain limitations, and misleading results are possible in certain cases. Suitability of material for direct compression is decided on the basis of index of good compressibility value, which is based on "r" values of the individual parameters. Substances having high "r" values will raise IGC value and vice versa. So suitability of a material should not be judged on the basis of IGC value. The incidence factor value should be considered, and outliers in "r" value of the individual factors, if present, should be properly addressed. Overall SeDeM-ODT expert system is an unmatched tool for material characterization at pre-formulation level and has significantly decreased time span and cost of pharmaceutical formulation development process.

Acknowledgements

We are thankful to Mr. Zahir Rahman (B. Pharm, M. Phil) Plant Manager, Ferozsons Laboratories Ltd., Nowshera, for his technical input and moral support.

Conflict of interest

The authors claim no conflict of interest.

Author details

Amjad Khan[1*], Shabnam Nazir[1], Hamad S. Alyami[2] and Aman Ullah[3]

1 Department of Pharmacy, Kohat University of Science and Technology (KUST), Kohat, Pakistan

2 Department of Pharmaceutics, Najran University, Najran, Saudi Arabia

3 Department of Pharmacy, Abasyn University, Peshawar, Pakistan

*Address all correspondence to: dr.amjad@kust.edu.pk

References

[1] Podczeck F, Al-Muti E. The tensile strength of bilayered tablets made from different grades of microcrystalline cellulose. European Journal of Pharmaceutical Sciences. 2010;**41**: 483-488

[2] Kasa P, Bajdik J, Zsigmond Z, Pintye-Hodi K. Study of the compaction behaviour and compressibility of binary mixtures of some pharmaceutical excipients during direct compression. Chemical Engineering and Technology. 2009;**48**:859-863

[3] Mazel V, Diarra H, Busignies V, Tchoreloff P. Comparison of different failure tests for pharmaceutical tablets: Applicability of the Drucker–Prager failure criterion. International Journal of Pharmaceutics. 2014;**470**:63-69

[4] Ofori-Kwakye K, Mfoafo KA, Kipo SL, Kuntworbe N, Boakye-Gyasi ME. Development and evaluation of natural gum-based extended release matrix tablets of two model drugs of different water solubilities by direct compression. SPJ. 2015;**24**(1):82-91. DOI: 10.1016/j.jsps.2015.03.005

[5] Mangwandi C, Zainal NA, Tao LJ, Glocheux Y, Albadarin AB. Investigation of influence of process variables on mechanical strength, size and homogeneity of pharmaceutical granules produced by fluidised hot melt granulation. Powder Technology. 2015; **272**:173-180

[6] Akseli I, Ladyzhynsky N, Katz J, He X. Development of predictive tools to assess capping tendency of tablet formulations. Powder Technology. 2013;**236**:139-148

[7] Sen M, Rogers A, Singh R, Chaudhury A, John J, Ierapetritou MG, et al. Flowsheet optimization of an integrated continuous purification processing pharmaceutical manufacturing operation. Chemical Engineering Science. 2013;**102**:56-66

[8] Vaidya MP, Avachat AM. Investigation of the impact of insoluble diluents on the compression and release properties of matrix based sustained release tablets. Powder Technology. 2011;**214**:375-381

[9] Desai PM, Liew CV, Heng PWS. Assessment of disintegration of rapidly disintegrating tablets by a visiometric liquid jet-mediated disintegration apparatus. International Journal of Pharmaceutics. 2013;**442**:65-73

[10] Singh R, Sahay A, Muzzio F, Ierapetritou M, Ramachandran R. A systematic framework for onsite design and implementation of a control system in a continuous tablet manufacturing process. Computers and Chemical Engineering. 2014;**66**:186-200. DOI: 10.1016/j.compchemeng.2014.02.029

[11] Sune-Negre JM, Perez-Lozano P, Minarro M, Roig M, Fuster R, Hernandez C, et al. Application of the SeDeM diagram and a new mathematical equation in the design of direct compression tablet formulation. European Journal of Pharmaceutics and Biopharmaceutics. 2008;**69**: 1029-1039

[12] 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 diagram expert system. International Journal of Pharmaceutics. 2014;**470**:15-27

[13] 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.

European Journal of Pharmaceutics and Biopharmaceutics. 2009;**73**:414-423

[14] Aguilar-Díaz JE, García-Montoya E, Suñe-Negre JM, Pérez-Lozano P, Miñarro M, Ticó JR. Predicting orally disintegrating tablets formulations of ibuprofen tablets: An application of the new SeDeM-ODT expert system. European Journal of Pharmaceutics and Biopharmaceutics. 2012;**80**:638-648

[15] ICH Topic Q8, Note for Guidance on Pharmaceutical Development, EMEA/CHMP/167068/2004; 2004

[16] The United States Pharmacopeia (USP-38/NF-33), General Chapter: <616> Bulk density and tapped density of powder page No. 420. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2015

[17] Font Q, Medicamenta P. Guía teórico práctica para farmacéuticos y medicos. 6th ed. Vol. 1. Barcelona: Labor Ed.; 1962. pp. 340-341

[18] The United States Pharmacopeia (USP-38/NF-33), General Chapter: <1174> Powder Flow, page No. 1326. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2015

[19] European Pharmacopoeia. 5th ed. Vol. 5.0. Strasbourg (France): Council of Europe; 2005. p. 2.9.16

[20] The United States Pharmacopeia (USP-38/NF-33), General Chapter: <731> Loss on drying, page no. 513. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2015

[21] European Pharmacopoeia. 5th ed. Vol. 5.1. Strasbourg (France): Council of Europe; 2005. p. 2.9.38

[22] European Pharmacopoeia. 7th ed. Vol. 7.2. Strasbourg (France): General Manograph <0478> Council of Europe; 2011

[23] The United States Pharmacopeia (USP-38/NF-33), General Chapter: <701> Disintegration, page no. 483. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2015

[24] Rowe RC, Sheshkey PJ, Quinn ME. Handbook of Pharmaceutical Excipients. 6th ed. London: Pharmaceutical press; 2009

[25] Alves-Silva I, Sá-Barreto LCL, Lima EM. M.S.S. Cunha-Filho pre formulation studies of itraconazole associated with benznidazole and pharmaceutical excipients. Thermochimica Acta. 2014;**575**:29-33

[26] Pilcer G, Amighi K. Formulation strategy and use of excipients in pulmonary drug delivery. International Journal of Pharmaceutics. 2010;**392**:1-19

[27] Jannin V, Rodier JD, Musakhanian J. Polyoxylglycerides and glycerides: Effects of manufacturing parameters on API stability, excipient functionality and processing. International Journal of Pharmaceutics. 2014;**466**:109-121

[28] Khan A, Iqbal Z, Rehman Z, Nasir F, Khan A, Ismail M, et al. Application of SeDeM expert system in formulation development of effervescent tablets by direct compression. SPJ. 2014;**22**: 433-444

[29] Millán SD, Suné-Negre JM, Pérez-Lozano P, Sarrate R, Fàbregas A, Carrillo C, et al. The use of the SeDeM diagram expert system for the formulation of captopril SR matrix tablets by direct compression. International Journal of Pharmaceutics. 2014;**461**:38-45

[30] Singh I, Kumar P. Pre formulation studies for direct compression suitability of cefuroxime and Paracetamol: A graphical presentation using SeDeM diagram. Acta Poloniae Pharmaceutica. 2012;**69**:87-93

[31] Khan A, Iqbal Z, Ibrahim M, Nasir F, Ullah Z. Prediction of the effect of taste masking on disintegration behavior, mechanical strength and rheological characteristics of highly water soluble drug (Itopride HCl); an application of SeDeM-ODT experts system. Powder Technology. 2015;**284**: 411-417. DOI: 10.1016/j.powtec.2015.06.062

[32] 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 Development and Industrial Pharmacy. 2019;**45**(9): 1537-1546. DOI: 10.1080/03639045.2019.1634094

[33] Suñé-Negre JM, Pérez-Lozano P, Roig M, Fuster R, Hernández C, Ruhí R, et al. Optimization of parameters of the SeDeM diagram expert system: Hausner index (IH) and relative humidity (%RH). European Journal of Pharmaceutics and Biopharmaceutics. 2011;**79**:464-472

[34] Perez P, Sune-Negre JM, Minarro M, Roig M, Fuster R, Garcıa-Montoya E, et al. A new expert systems (SeDeM diagram) for control batch powder formulation and pre formulation drug products. European Journal of Pharmaceutics and Biopharmaceutics. 2006;**64**:351-359

[35] Aguilar-Diaz JE, Garcıa-Montoya E, Perez-Lozano P, Sune-Negre JM, Minarro M, Tico JR. SeDeM expert system a new innovator tool to develop pharmaceutical forms. Drug Development and Industrial Pharmacy. 2014;**40**(2):222-236. DOI: 10.3109/03639045.2012.756007