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SeDeM Diagram: A New Expert System for the Formulation of Drugs in Solid Form

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1. Introduction

The SeDeM expert system is a methodology which is applied in preformulation and formulation studies of medicines specifically in solid dosage forms. This system informs on the physical profile of powdered substances (APIs and excipients) used to formulate drugs (Suñé et al, 2005; García et al, 2010; Aguilar et al, 2009). By determining whether powders (API or excipient) are suitable for direct compression, the SeDeM profile will inform about the advantages and gaps of those powdered substance to be used in direct compression, so the system informs on whether the direct compression method is appropriate (e.g.. wet granulation should be applied before compression).
The characterization of powdered substances by SeDeM facilitates the identification of the characteristics that require amendment in order to obtain tablets by direct compression. This system thus provides information that will ensure the robust design of the formulation in the final product.
This new method is based on the selection and application of several parameters that the formulation must fulfill to ensure a successful tablet elaborated by direct compression. The following criteria are applied:

a. The formulation must be representative and appropriate for the requirements of compression technology.
b. The execution of the experimental methodology and calculus must be readily applicable.

2. Parameters examined by the SeDeM method

SeDeM uses 12 tests (Suñé et al, 2005; García et al, 2010; Aguilar et al, 2009) to examine whether a powder is suitable for direct compression.

- Bulk density (Da)
- Tapped density (Dc)
- Inter-particle porosity (Ie)
- Carr index (IC)

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- Cohesion index (Icd)
- Hausner ratio (IH)
- Angle of repose (α)
- Flowability (t″)
- Loss on drying (%HR)
- Hygroscopicity (%H)
- Particle size (%Pf)
- Homogeneity index (Iθ)

These tests are grouped into five factors on the basis of the physical characteristics of the powder and the functionality of the drug:

Dimensional Parameter. Bulk density (Da) and Tapped density (Dc). These affect the size of the tablet and its capacity to pile up. In addition, these tests are used in the calculus of other mathematical indexes for the determination of the compression parameter.

Compressibility Parameter. Inter-particle porosity (Ie), Carr index (IC) and Cohesion index (Icd). These affect the compressibility of the powder.

Flowability/Powder Flow Parameter. Hausner ratio (IH), Angle of repose (α) and Flowability (t″). These influence the flowability of the powdered substance when compressed.

Lubricity/Stability Parameter. Loss on drying (%HR) and Hygroscopicity (%H). These affect the lubricity and future stability of the tablets.

Lubricity/Dosage parameter. % Particles < 50 µm and Homogeneity Index. These influence the lubricity and dosage of the tablets.

Table 1 shows the 5 parameters, with the abbreviations, units, formulas and incidence on compression.

Incidence factor	Parameter	Symbol	Unit	Equation
Dimension	Bulk Density	Da	g/ml	Da = P/Va
	Tapped Density	Dc	g/ml	Dc = P/Vc
Compressibility	Inter-particle Porosity	Ie	–	Ie = Dc − Da/Dc × Da
	Carr Index	IC	%	IC = (Dc − Da/Dc) 100
	Cohesion Index	Icd	N	Experimental
Flowability/Powder Flow	Hausner Ratio	IH	–	IH = Dc/Da
	Angle of Repose	(α)	°	tg α = h/r
	Powder Flow	t″	s	Experimental
Lubricity/Stability	Loss on Drying	%HR	%	Experimental
	Hygroscopicity	%H	%	Experimental
Lubricity/Dosage	Particles < 50 µm	%Pf	%	Experimental
	Homogeneity Index	(Iθ)	–	* Iθ = Fm / 100 + Δ Fmn

Table 1. Parameters and tests used by the SeDeM method.

2.1 Experimental procedure used to study a powdered substance with parameters considered by the SeDeM method

Pharmacopoeia methodologies are used to calculate these parameters. When this is impossible, a common strategy used in pharmaceutical technology development is applied. The methods used for each test are described below (Pérez et al, 2006):

- Bulk density (Da): The method is described in Section 2.9.34 of Eur. Ph. (Ph Eur, 2011)
- Tapped density (Dc): The method is described in Section 2.9.34 of Eur. Ph. (Ph Eur, 2011) The volume taken is the value obtained after 2500 strokes using a settling apparatus with a graduated cylinder (voluminometer).
- Inter-particle porosity (Ie) of the powder mixture (Font, 1962) is calculated from the following equation: $Ie=Dc-Da/Dc\times Da$
- Carr index (IC%) (Córdoba et al, 1996; Rubinstein, 1993; Torres & Camacho, 1991; Wong, 1990). The method is described in Section 2.9.34 of Eur. Ph. (Ph Eur, 2011) This is calculated from Da and Dc as: $IC=(Dc-Da/Dc)100$
- Cohesion index (Icd): This index is determined by compressing the powder, preferably in an eccentric press. The mean hardness (N) of the tablets is calculated. First, the raw powder is tested, but if it cannot be compressed, 3.5% of the following mixture is added to the mix: talc 2.36%, Aerosil® 200 0.14% and magnesium stearate 1.00%.
- Hausner ratio (IH) (Ph Eur, 2011; Rubinstein, 1993). The method is described in Section 2.9.34 of Eur Ph (Ph Eur, 2011). This is calculated from Da and Dc as: $IH=Dc/Da$
- Angle of repose (α) (Rubinstein, 1993, Muñoz, 1993). The method is described in Section 2.9.36 of Eur Ph (Ph Eur, 2011). This is the angle of the cone formed when the product is passed through a funnel with the following dimensions: height 9.5 cm, upper diameter of spout 7.2 cm, internal diameter at the bottom, narrow end of spout 1.8 cm. The funnel is placed on a support 20 cm above the table surface, centred over a millimetre-grid sheet on which two intersecting lines are drawn, crossing at the centre. The spout is plugged and the funnel is filled with the product until it is flush with the top end of the spout when smoothed with a spatula. Remove the plug and allow the powder to fall onto the millimetre sheet. Measure the four radii of the cone base with a slide calliper and calculate the mean value (r). Measure the cone height (h). Deduce α from $\tan(\alpha)=h/r$.
- Flowability (t''): The method is described in Section 2.9.16 of Eur. Ph (Ph Eur, 2011). It is expressed in seconds and tenths of a second per 100 grams of sample, with a mean value of three measurements.
- Loss on drying (%HR): This is measured by the method described in 2.2.32 in Eur. Ph (Ph Eur, 2011). The sample is dried in an oven at 105 °C ± 2 °C, until a constant weight is obtained.
- Hygroscopicity (%H): Determination of the percentage increase in sample weight after being kept in a humidifier at a relative humidity of 76% (±2%) and a temperature of 22°C± 2°C for 24 h.
- Percentage of particles measuring <50 µm (%Pf): Particle size is determined by means of the sieve test following the General method 2.9.12 of Eur. Ph. (Ph Eur, 2011). The value returned is the % of particles that pass through a 0.05-mm sieve when vibrated for 10 min at speed 10 (CISA vibrator).
- Homogeneity index (Iθ): This is calculated according to the General method 2.9.12 of Eur. Ph (Ph Eur, 2011).To determine particle size by means of the sieve test, the grain size of a 100g sample is measured by subjecting a sieve stack to vibration for 10 min at speed 10 (CISA vibrator). The sieve sizes used are 0.355 mm, 0.212 mm, 0.100 mm and 0.05 mm. The percentage of product retained in each sieve is calculated and the amount that passes through the 0.05mm sieve is measured. The percentage of fine particles (<50 µm) (%Pf) was calculated as described above. Note that if this 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 <50 µm particles found may be lower than the true figure. The following equation is then applied to the data obtained.

$$*I\theta = \frac{Fm}{100 + (dm - dm\text{-}1)Fm\text{-}1 + (dm+1 - dm)Fm+1 + (dm - dm\text{-}2)Fm\text{-}2 + (dm+2 - dm)Fm+2 + ... + (dm - dm\text{-}n)Fm\text{-}n + (dm+n - dm)Fm+n} \quad (1)$$

Where:

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

2.2 Determination of acceptable limit values for each parameter included by the SeDeM method

Having obtained the values as described above, certain limits are set (Table 2) on the basis of the parameters chosen and the values described in the Handbook of Pharmaceutical Excipients (Kibbe, 2006), or alternatively on the basis of experimental tests.

Incidence	Parameter	Acceptable range
Dimension	Bulk density	0–1 g/ml
	Tapped density	0-1 g/ml
Compressibility	Inter-particle porosity	0–1.2
	Carr index	0–50 (%)
	Cohesion index	0–200 (N)
Flowability/powder flow	Hausner ratio	3–1
	Angle of repose	50–0 (°)
	Powder flow	20–0 (s)
Lubricity/stability	Loss on drying	0-10 (%)
	Higroscopicity	20–0 (%)
Lubricity/dosage	Particles < 50 µ	50–0 (%)
	Homogeneity index	0–2 × 10−2

Table 2. Limit values accepted for the SeDeM Diagram parameters.

The rationale to establish the limits for each parameter is:

- Da, Dc, Ie e IC are calculated from the extreme values (excluding the most extreme values) described in "Handbook of Pharmaceutical Excipients" (Kibbe, 2006). For the

Carr Index, limits are based on references in "Tecnologia Farmaceutica" by S. Casadio (Casadio, 1972) and on monograph 2.9.36 of Ph Eur (Ph Eur, 2011).

- Icd. The limit is determined empirically from compression tests on many powdered substances, based on the maximum hardness obtained without producing capped or broken tablets. This hardness is then established as the maximum limit. The minimum value is "0". This value implies that no tablets are obtained when the powders are compressed.
- IH, Powder flow, repose angle. The limits are set on the basis of the monographs described in "Handbook of Pharmaceutical Excipients" (Kibbe, 2006), and monograph 2.9.36 of Ph Eur (Ph Eur, 2011) or other references in "Tecnologia Farmaceutica" by S. Casadio (Casadio, 1972).
- %HR. The limits are established on the basis of the references cited elsewhere, such as "Farmacotecnia teórica y práctica" by José Helman (Helman, 1981). The optimum humidity is between 1% to 3%.
- Hygroscopicity is based on the "Handbook of Pharmaceutical Excipients" (Kibbe, 2006): based on manitol (not hygroscopic) and sorbitol (highly hygroscopic).
- Particle size. The limits are based on the literature. These sources (Kibbe, 2006) report that rheological and compression problems occur when the percentage of fine particles in the formulation exceeds 25%.

The limits for the Homogeneity Index (Iθ) are based on the distribution of the particles of the powder (see Table 3, indicating the size of the sieve (in mm), average particle size in each fraction and the difference in average particle size in the fraction between 0.100 and 0.212 and the others). A value of 5 on a scale from 0 to 10 was defined as the minimum acceptable value (MAV), as follows:

Sieve (mm)	Corresponding fraction	Average of the diameter of the fraction	Corresponding diameter (dm ... dm ± n)	Dif dm with the mayor component
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. Distribution of particles in the determination of Iθ.

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 MAV 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.

2.3 Conversion of the limits considered in each parameter of the SeDeM method into the radius (r) of the SeDeM Diagram

The numerical values of the parameters of the powder, which are obtained experimentally (v) as described above, are placed on a scale from 0 to 10, considering 5 as the MAV.

Incidence	Parameter	Limit value (v)	Radius (r)	Factor applied to v
Dimensions	Bulk density	0–1	0–10	10v
	Tapped density	0–1	0–10	10v
Compressibility	Inter-particle porosity	0–1.2	0–10	10v/1.2
	Carr index	0–50	0–10	v/5
	Cohesion index	0–200	0–10	v/20
Flowability/powder flow	Hausner ratio (a)	3–1	0–10	(30-10v)/2
	Angle of repose	50–0	0–10	10 − (v/5)
	Powder flow	20–0	0–10	10 − (v/2)
Lubricity/estability	Loss on drying (b)	10-0	0-10	10-v
	Higroscopicity	20–0	0–10	10 − (v/2)
Lubricity/dosage	Particles < 50 µ	50–0	0–10	10 − (v/5)
	Homogeneity index	0–2 × 10−2	0–10	500v

Table 4. Conversion of limits for each parameter into radius values (r).
(a) The values that exceptionally appear below 1 are considered values corresponding to non-sliding products.
(b) 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 behaviour 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 favouring the adhesion to punches and dyes. Consequently, it was considered that this parameter should present optimal experimental values from 1% to 3% (Braidotti, 1974). 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 (Suñé et al, 2011).

The correspondence of the value of the parameters with this scale takes into account the limit values (see 2.2), using the factors indicated in Table 4. When all radius values are 10, the SeDeM Diagram takes the form of a circumscribed regular polygon, drawn by connecting all the radius values of the parameters with linear segments. Table 4 shows the factors used for calculating the numerical value of each parameter required for the SeDeM method.

2.4 Graphical representation of the SeDeM Diagram

When all radius values are 10, the SeDeM Diagram takes the form of a circumscribed regular polygon, drawn by connecting the radius values with linear segments. The results obtained from the earlier parameter calculations and conversions are represented by the radius. The figure formed indicates the characteristics of the product and of each parameter that determines whether the product is suitable for direct compression. In this case, the SeDeM Diagram is made up of 12 parameters, thus forming an irregular 12-sided polygon (Figure 1).

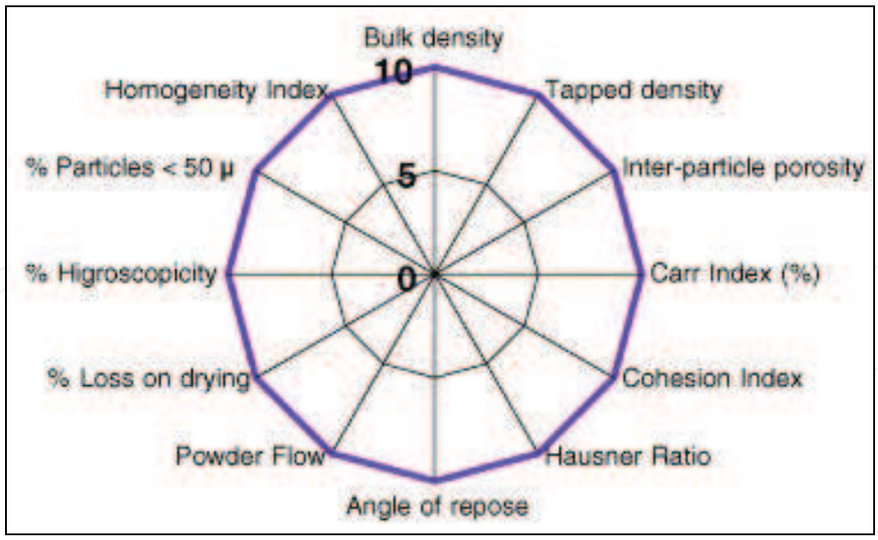

Fig. 1. The SeDeM Diagram with 12 parameters.

2.5 Acceptable limits for Indexes

To determine whether the product is suitable for direct compression using a numerical method, the following indexes are calculated based on the SeDeM Diagram as follows:

$$\text{– Parameter index} \quad \text{IP}=\frac{\text{n°P} \geq 5}{\text{n°Pt}} \tag{2}$$

Where:
No. p ≥ 5: Indicates the number of parameters whose value is equal to or higher than 5
No. Pt: Indicates the total number of parameters studied
The acceptability limit would correspond to:

$$IP = \frac{n^{o}\, P \geq 5}{n^{o}\, Pt} = 0{,}5 \tag{3}$$

$$\text{– Parameter profile Index} \quad \text{IPP} = \text{Average of}\left(\text{r}\right) \text{ all parameters} \tag{4}$$

Average (r) = mean value of the parameters calculated.
The acceptability limit would correspond to: IPP = media (r) = 5

$$\text{– Good Compressibility Index} \quad \text{IGC=IPP x f} \tag{5}$$

$$\text{f} = \quad \text{Reliability factor} = \frac{\text{Polygon area}}{\text{Circle area}} \tag{6}$$

The acceptability limit would correspond to: ICG = IPP x f = 5.
The reliability factor indicates that the inclusion of more parameters increases the reliability of the method (Figure 2).

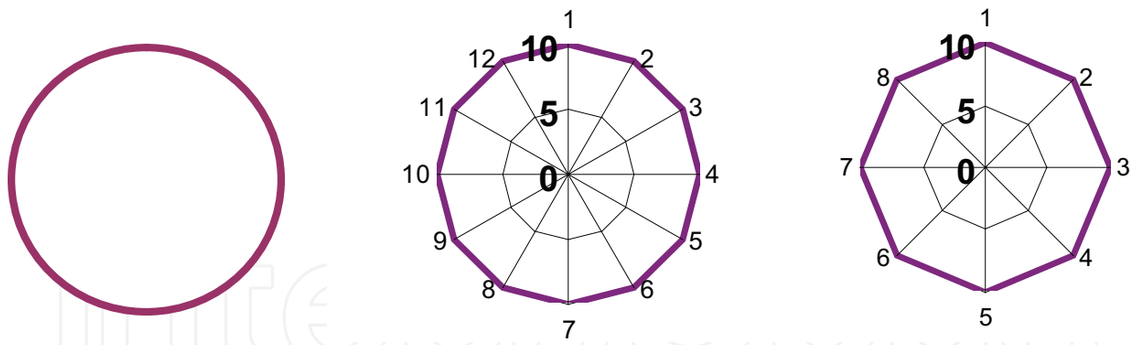

Fig. 2. On the left graph with ∞ parameters (maximum reliability), f = 1. In the center, graph with 12 parameters (nº of parameters in this study), f = 0.952. On the right, graph with 8 parameters (minimum reliability), f = 0.900.

3. Practical applications of SeDeM

3.1 Determination of the suitability of an API to be subjected to direct compression technology

Here we 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, applying the profile to the SeDeM Diagram.

We measured the 12 parameters proposed in the SeDeM method following the procedures indicated. Thus we obtained the values on which the factors set out in Table 5 are applied to obtain the numerical values corresponding to the radius of the diagram and the values of the mean incidence. All the values in Table 5 correspond to the average of two determinations. The radius values are represented in the diagram shown in Figure 3.

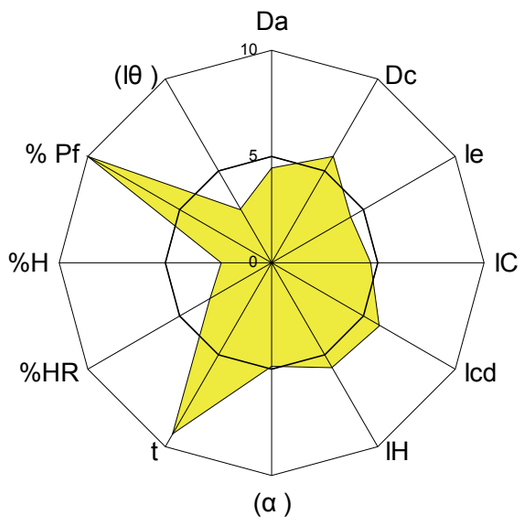

Fig. 3. SeDeM Diagram for API SX-325.

To obtain the indices of acceptance or qualification for formulation by direct compression, the formulas corresponding to the parametric index were applied from the numerical results of the radius shown in Table 5. The results of the acceptance indices are shown in Table 6.

Incidence factor	Parameter	Symbol	Unit	Value (v)	(r)	Mean incidence
Dimension	Bulk Density	Da	g/ml	0.448	4.48	5.16
	Tapped Density	Dc	g/ml	0.583	5.83	
Compressibility	Inter-particle Porosity	Ie	–	0.517	4.31	4.95
	Carr Index	IC	%	23.156	4.63	
	Cohesion Index	Icd	N	118.00	5.90	
Flowability/Powder Flow	Hausner Ratio	IH	–	1.868	5.66	6.59
	Angle of Repose	(α)	°	25.770	4.85	
	Powder Flow	t	s	1.500	9.25	
Lubricity/Stability	Loss on Drying	%HR	%	5.650	4.35	3.37
	Hygroscopicity	%H	%	15.210	2.40	
Lubricity/Dosage	Particles < 50 µm	%Pf	%	0.000	10.0	6.45
	Homogeneity Index	(Iθ)	–	0.0058	2.90	

Table 5. Application of the SeDeM method to API in powder form (API SX-325), and calculation of radii.

Parameter index		0.42	
Parametric profile index (mean r of all parameters)		5.38	
Good compression index (IGC)		5.12	

Table 6. SeDeM acceptance index for API SX-325

On the basis of the results of the radius corresponding to the SeDeM Diagram, the parametric profile was > 5. This value implies that API SX-325 is suitable for direct compression. However, in order to discern the appropriateness of this substance for this formulation technology, we analyzed the 5 groups of individual factors classified by the type of incidence in this compression.

In the case study above, only the parameters involved in the general factor of denominated incidence lubrication/stability presented values below 5 (median = 3.37). This finding implies deficient rheological qualities and poor stability, expressed by a high intrinsic humidity of balance and high hygroscopicity. The product tended to capture humidity, thus worsening the rheological profile (compression, lack of flow) and consequently impairing its stability. These deficiencies are reflected graphically in the SeDeM Diagram, which shows that a large shaded area (activity area) (the greater the shaded area, the more suitable the characteristics for direct compression) is present for most of the parameters. However, some parameters show a small shaded area, thus indicating that the powder is not suitable for direct compression.

In this regard, the SeDeM method informed (table 5) on the following for API SX-325: it is a dusty substance with correct dimensional characteristics (Da and Dc); it shows moderately acceptable compressibility (IE, IC, Icd), which can be improved with the addition of excipients of direct compression (DC); it shows very good fluidity/flowability (IH, α, t'') and correct lubrication/dosage (%Pf, Iθ). Given these characteristics API SX-325 is suitable for compression with the addition of standardized formula of lubricant. The group of factors with deficient incidence corresponds to lubricity/stability and, considering the parameters HR and H, corrective measures can be taken to prevent its negative influence on direct compression. These measures include drying the material and preparing the tablet in rooms with controlled relative humidity below 25%.

The results given by the SeDeM method in this example demonstrate that it is reliable in establishing whether powdered substances have suitable profiles to be subjected to direct compression. Consequently, SeDeM is a tool that will contribute to preformulation studies of medicines and help to define the manufacturing technology required. Indeed, the application of the SeDeM Diagram allows the determination of the direct compression behaviour of a powdered substance from the index of parametric profile (IPP) and the index of good compression (IGC), in such a way that an IPP and an IGC equal or over 5 indicates that the powder displays characteristics that make it suitable for direct compression, adding only a small amount of lubricant (3.5% of the magnesium stearate, talc and Aerosil® 200). Also, with IPP and IGC values between 3 and 5, the substance will require a DC diluent excipient suitable for direct compression. In addition, it is deduced that techniques other than direct compression (wet granulation or dry granulation) will be required for APIs with IPP and IGC values below 3.

The SeDeM Diagram is not restricted to active products since it can also be used with new or known excipients to assess their suitability for application as adjuvants in direct compression. Thus, knowledge of excipient profiles, with their corresponding parameters, will allow identification of the most suitable excipient to correct the characteristics of APIs registering values under 5.

Of note, the greater the number of parameters selected, the greater the reliability of the method, in such a way that to obtain a reliability of the 100%, the number of parameters applied would have to be infinite (reliability factor = 1). The number of parameters could be extended using additional complementary ones, such as the true density, the index of porosity, the electrostatic charge, the specific surface, the adsorption power, % of lubrication, % friability, and the index of elasticity. However, while improving the reliability of the method, the inclusion of further parameters would be to the detriment of its simplicity and rapidity, since complementary parameters are difficult to apply.

3.2 Application of the SeDeM method to determine the amount of excipient required for the compression of an API that is not apt for direct compression

Experimental determination of the parameters of the SeDeM method for a range of APIs and excipients allows definition of their corresponding compressibility profiles and their subsequent mathematical treatment and graphical expression (SeDeM Diagram). Various excipient diluents can be analyzed to determine whether a substance is appropriate for direct compression and the optimal proportion of excipient required to design a suitable formulation for direct compression based on the SeDeM characteristics of the API (Suñé et al, 2008a). In this regard, the SeDeM method is a valid tool with which to design the formulation of tablets by direct compression.

The mathematical equation can be applied to the 5 parameters (dimension, compressibility, flowability/powder flow, lubricity/stability lubricity/dosage) considered deficient by the SeDeM system. The mathematical equation is applied to correct a deficient parameter of the API. The equation proposed (Equation 7) allows calculation of the amount of excipient required to compress the API on the basis of the SeDeM radius considered minimum (5) for each parameter of incidence that allows correct compression.

$$CP = 100 - \left(\frac{RE - R}{RE - RP} \times 100 \right) \tag{7}$$

Where:

CP = % of corrective excipient

RE = mean-incidence radius value (compressibility) of the corrective excipient
R = mean-incidence radius value to be obtained in the blend
RP = mean-incidence radius value (compressibility) of the API to be corrected
The unknown values are replaced by the calculated ones required for each substance in order to obtain R = 5 (5 is the minimum value considered necessary to achieve satisfactory compression). For example, if a deficient compressibility parameter for an API requires correction, Equation 7 is applied by replacing the terms RE and RP with the values calculated for each substance with the purpose to obtain a R=5, thus obtaining the optimal excipient to design a first drug formulation and the maximum amount required for a comprehensive understanding of the proposed formula. From this first formulation, research can get underway for the final optimization of the formulation, taking into consideration the biopharmaceutical characteristics required in the final tablet (disintegration, dissolution, etc). We thus present a method to establish the details of the formulation of a given drug by direct compression.

3.2.1 Practical application of the mathematical equation to calculate the amount of excipient required for a deficient API to be subjected to direct compression technology

When an API requires an appropriate formula for the direct compression, it must be characterized following the SeDeM Diagram. Furthermore, a series of excipients used for DC are also characterized using the diagram. If the API has deficient compressibility parameters (<5), it is mixed with an excipient with a satisfactory compressibility parameter (>5), thereby correcting the deficiency. The excipient that shows the smallest amount to correct this parameter should be used. The amount of excipient is determined by the mathematical equation of the SeDeM system (Equation 7).
Here we describe an example using an API 842SD and 6 diluents used for DC. The corresponding parameters and the radius mean values obtained with samples of this substance are shown in Table 7 and the parameters and the radius mean values of six excipient diluents used in DC are shown in Table 8 (Suñé et al, 2008a).

Incidence factor	Parameter	Symbol	Unit	Value (v)	(r)	Mean incidence
Dimension	Bulk Density	Da	g/ml	0.775	7.75	8.88
	Tapped Density	Dc	g/ml	1.140	10.00	
Compressibility	Inter-particle Porosity	Ie	–	0.413	3.44	3.40
	Carr Index	IC	%	32.018	6.40	
	Cohesion Index	Icd	N	7.330	0.37	
Flowability/Powder Flow	Hausner Ratio	IH	–	1.98	5.10	4.15
	Angle of Repose	(α)	°	37.450	2.51	
	Powder Flow	t	s	10.330	4.84	
Lubricity/Stability	Loss on Drying	%HR	%	9.865	0.68	5.34
	Hygroscopicity	%H	%	0.007	10.0	
Lubricity/Dosage	Particles < 50 µm	%Pf	%	12.000	7.60	4.40
	Homogeneity Index	(Iθ)		0.0024	1.20	
Parameter index				0.50		
Parametric profile index (mean r of all parameters)				4.99		
Good compression index (IGC)				4.75		

Table 7. Parameters, mean incidence and parametric index for API 842SD

Table 8. Radius parameters, mean incidence and parametric index for excipients DC

	PARAMETERS (radius)												FAC		
Excipient	Da	Dc	Ie	IC	Icd	IH	α	t"	%HR	%H	%pf	(Iθ)	Dimension.	Compressibility	Flowability / Powder Flow
Avicel PH 101 Batch 6410C	3.47	4.63	6.02	5.01	10.00	5.55	3.46	0.00	3.84	8.17	3.38	10.00	4.05	7.01	3.01
Isomalt® Batch LRE 539	4.40	5.60	4.06	4.29	10.00	5.76	6.24	6.85	4.01	9.89	9.00	2.00	5.00	6.11	6.28
Kleptose® Batch 774639	5.58	8.46	5.08	6.81	10.00	4.95	3.51	6.50	0.00	8.12	3.60	1.90	7.02	7.30	4.98
Kollindon® VA64 Batch 28-2921	2.53	3.43	8.64	5.25	6.91	5.48	6.04	5.25	3.19	2.85	8.40	5.50	2.98	6.93	5.59
Plasdone ®S630 Batch 6272473	2.48	3.73	10.00	6.70	10.00	4.99	4.13	0.00	3.46	3.17	3.60	5.70	3.11	8.90	3.04
Prosolv® HD90 Batch K950044	4.86	5.96	3.17	3.69	10.00	5.91	5.99	6.75	3.44	8.86	6.24	10.00	5.41	5.62	6.22

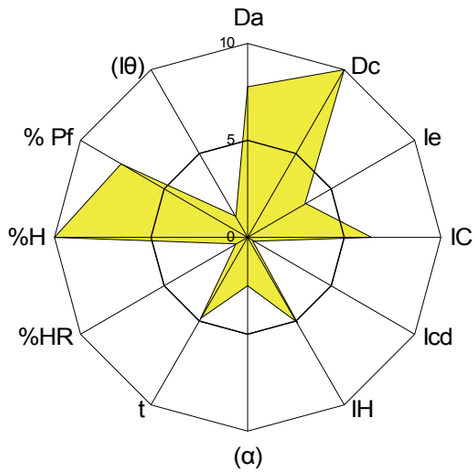

Fig. 4. SeDeM Diagram for API 842SD

The SeDeM Diagram for API 842SD (Figure 4, Table 7) indicates that this substance has deficient compressibility (r=3.40), limited rheological characteristics (r=4.15) and low lubricity/dosage (r=4.40). Consequently, to apply direct compression to API 842SD, it requires formulation with an excipient that enhances the compressibility factor. This excipient is identified by the SeDeM system.

In order to select the excipient and the concentration used to correct the deficiencies and, in particular, the compressibility, we applied the mathematical equation of the SeDeM Expert system (Equation 7): replacing the unknowns (RE and RP) with the values calculated for each substance (RE for excipients and RP for API) with aim to obtain R=5. The results obtained are shown in Table 9.

EXCIPIENT	Avicel® PH101	Kleptose®	Koll VA®	Plasdone® S630	Prosolv® HD90	Isolmalt® 721
RE	7.01	7.30	6.93	8.90	5.62	6.11
RP (API)	3.40	3.40	3.40	3.40	3.40	3.40
R	5.00	5.00	5.00	5.00	5.00	5.00
% excipient	44.32	41.03	45.33	29.09	72.07	59.04

Table 9. Amount of excipient required to be mixed with the API to obtain a compressibility factor equal to 5.

Plasdone S630 was the most suitable excipient to correct the deficit (compressibility) of API 842SD with the lowest concentration (29.09 %). (Table 9)

To better understand the SeDeM system, the graphical representations of the profiles of the API and the excipient can be superposed. Figure 5 shows how the deficiencies of an API would be compensated when formulated. The green line corresponds to the excipient that theoretically provides the final mixture the characteristics to be compressed. In this way, the information provided by the SeDeM system allows the formulator to start working with excipients that have a high probability to provide suitable formulations, thus reducing the lead time of formulation.

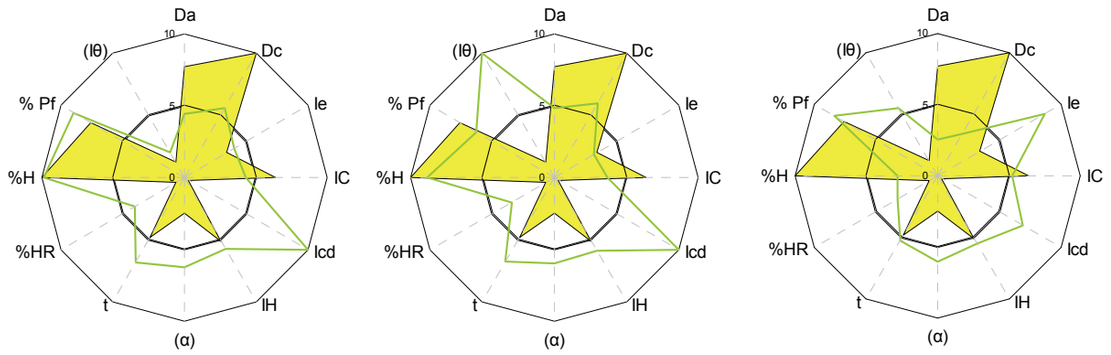

Fig. 5. Green indicates the part that corresponds to the excipient that provides suitable compressibility to the final mixture with the API (in yellow). Three excipients are shown, all of them covering the deficiencies of the API.

3.3 Application of the SeDeM system to the quality control of batches of a single API or excipient used for direct compression

The SeDeM system is also apt for verification of the reproducibility of manufacturing standards between batches of the same powdered raw material (API or excipient). Indeed, superposing the SeDeM Diagrams of each batch, the degree of similarity or difference between the same API on the basis of the established parameters can determine its appropriateness for compression.

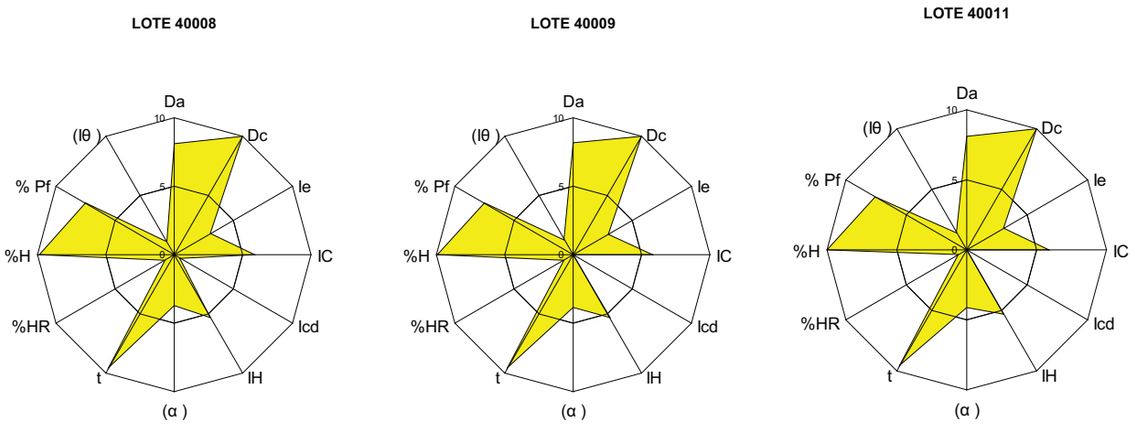

Fig. 6. SeDeM Diagram of 3 batches of API FO130.

The SeDeM method is also a useful tool for the study of the reproducibility of a manufacturing method used for a powdered substance and, thus of the validation of systematic variation during elaboration. A manufacturing process gives rise to variations in the final product and these variations must fall within limits or established specifications. By applying the SeDeM method to study reproducibility between batches of the same API or excipient, specifications in the different parameters can be established to ensure the same quality of the product regardless of the batch analyzed. In addition, these specifications must be used for the establishment of particular limits for quality control applications. To achieve this goal it is necessary to study the parameters of the SeDeM Diagram, applying the same statistic analyses required to establish the

pharmacotechnical equivalence between batches. Correct reproducibility between batches will ensure the reproducibility and the quality of the tablets formulated with this API or excipient, regardless of the batch used.

Figure 6 shows the SeDeM Diagrams of three batches from the same API (Perez et al, 2006). In this case the mark and the indices were very similar. This control has the advantage that the method has the capacity to detect variations in particle size between batches of the product. This capacity thus contributes to the formulation of the pharmaceutical forms and their correct dissolution.

3.4 Application of the SeDeM method to differentiate the excipient in the same chemical family

The SeDeM system also allows differentiation between excipients of the same chemical family but that differ in physical characteristics. These characteristics will determine their use in a formulation for direct compression of a given API. In a previous study (Suñé et al, 2008b) several lactoses were characterized, and in figure 7 can be observed the clear differentiation that makes the SeDeM methodology between the same chemical substances (but different functionally).

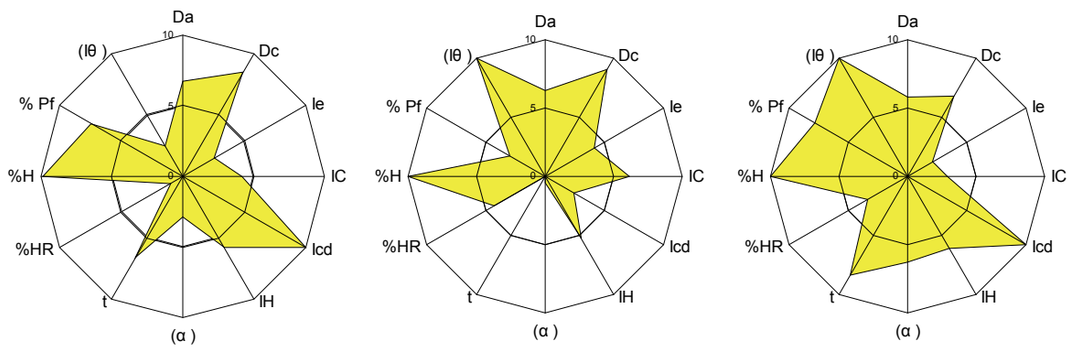

Fig. 7. SeDeM Diagram for three kinds of lactose. On the left: Lactose anhydre IGC: 5.39. In the center: Lactose monohydrate IGC: 4.83. On the right: Lactose fast-flow IGC: 6.30.

3.5 Application of the SeDeM Diagram to differentiate excipients of the same functional type

Also, the SeDeM Expert system allows differentiation between excipients from the same functional type, for example disintegrants or diluents. In the former, the SeDeM characterization provides the information required to predict the difficulties encountered for compression.

By quantifying the 12 tests provided by the system, the deficient values for their compression can be defined; on the basis of these values, an adequate (applying the same SeDeM Diagram) substance can be selected to improve the compressibility in the final mixture of the disintegrants and the API. Figure 8 shows the characterization of several disintegrants using the SeDeM technique, where the differences between each one in relation to their major or minor compression capacity are shown, although all are used because of their disintegrant function (Aguilar et al, 2009).

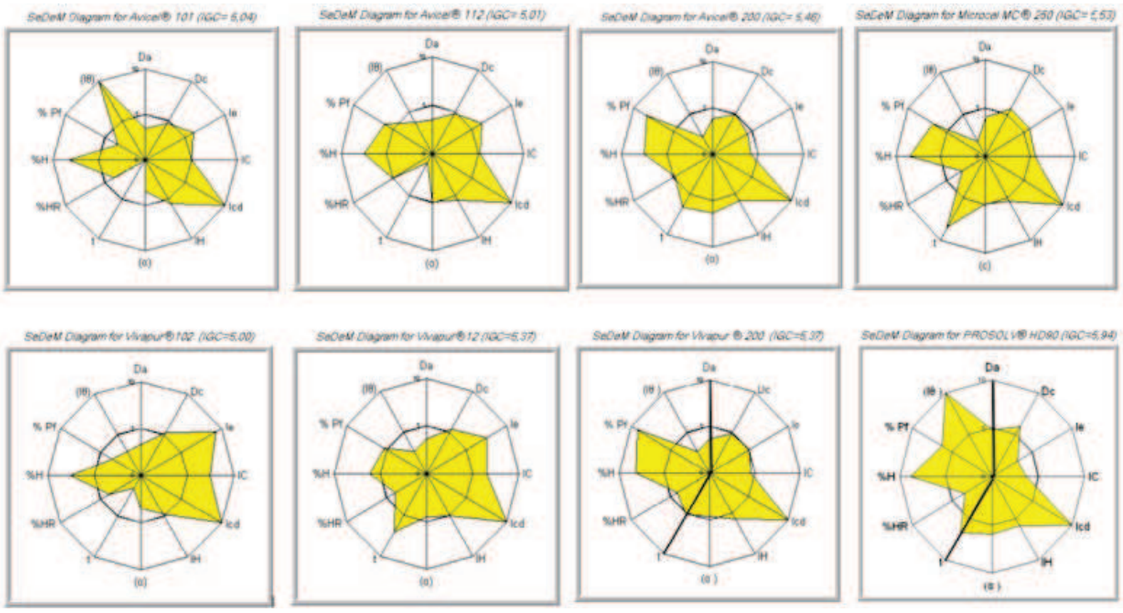

Fig. 8. SeDeM diagram for several disintegrant excipients.

3.6 The new model SeDeM-ODT to develop orally disintegrating tablets by direct compression

This innovative tool is the new SeDeM-ODT model which provides the Index of Good Compressibility & Bucodispersibility (IGCB index) obtained from the previous SeDeM method (Aguilar et al, 2011). The IGCB index is composed by 6 factors that indicate whether a mixture of powder lends itself to be subjected to direct compression. Moreover, the index simultaneously indicates whether these tablets are suitable as bucodispersible tablet (disintegration in less than 3 minutes). The new factor, disgregability (Table 10), has three parameters that influence this parameter. The graph now comprises 15 parameters (Figure 9).

Factor	Parameter	Limit value (v)	Radius
Disgregability	Effervescence	0-5 (minutes)	10-0
	Disintegration Time with disc (DCD)	0-3(minutes)	10-0
	Disintegration Time without disc (DSD)	0-3 (minutes)	10-0

Table 10. The new factor disgregability is added to the SeDeM expert system to achieve the SeDeM-ODT expert system.

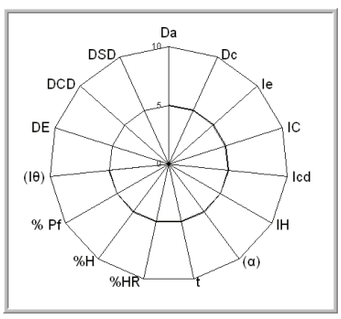

Fig. 9. SeDeM-ODT Diagram

4. Conclusions

Here we developed an original methodology for the preformulation and powder substance characterization. This method facilitates studies on the design and development of formulations for the production of tablets by direct compression. The SeDeM expert system is a useful tool because, in addition to considering the type of components, it also provides recommendations on intrinsic properties, such as the characteristics and morphology of the particles. We propose that given the accuracy of the information provided by this system, formulations will have a higher probability of being successfully compressed.

This method characterizes the individual components of a formulation and applies a mathematical analysis to determine the exact amount of each in the final formulation.

The formulation provided will be valid for direct compression. This manufacturing procedure offers many advantages from a production perspective. In addition to being faster than other techniques, it is straightforward as it reduces the number of steps during the manufacturing process.

In addition SeDeM has the advantage of providing formulation with the lowest amount of excipients as it combines the API with only one excipient and the standard formula of lubricants, thus avoiding the used of unnecessary excipients, such as diluents, binders and agglutinants.

The information given by the SeDeM system contributes to a Quality by Design Development. Consequently, this innovative tool is consistent with the current requirements of regulatory health authorities such as the FDA and ICH.

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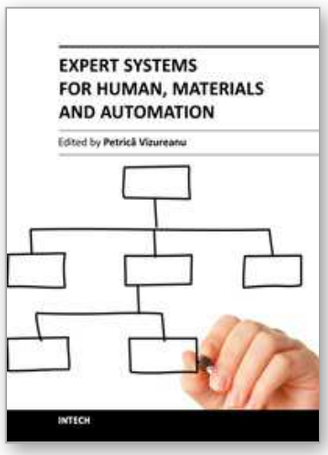

Expert Systems for Human, Materials and Automation

Edited by Prof. PetricÄƒ Vizureanu

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The ability to create intelligent machines has intrigued humans since ancient times, and today with the advent of the computer and 50 years of research into AI programming techniques, the dream of smart machines is becoming a reality. The concept of human-computer interfaces has been undergoing changes over the years. In carrying out the most important tasks is the lack of formalized application methods, mathematical models and advanced computer support. The evolution of biological systems to adapt to their environment has fascinated and challenged scientists to increase their level of understanding of the functional characteristics of such systems. This book has 19 chapters and explain that the expert systems are products of the artificial intelligence, branch of computer science that seeks to develop intelligent programs for human, materials and automation.

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