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Research paper

# A new expert systems (SeDeM Diagram) for control batch powder formulation and preformulation drug products

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**Abstract**

The new SeDeM Method is proposed for testing the batch-to-batch reproducibility of the same active pharmaceutical ingredient (API) in powder form. The procedure describes the study of the galenic properties of substances in powder form in terms of the applicability of direct compression technology. Through experimental determination of the SeDeM Method parameters, and their subsequent mathematical treatment and graphical expression (SeDeM Diagram), three batches of the same API were analysed to determine whether it was suitable for direct compression. Batch-to-batch reproducibility of the results was verified. It was concluded that the SeDeM Method is suitable for testing batch-to-batch reproducibility of characteristics in powdered APIs substances. The results obtained confirm that the SeDeM Method is a useful, effective tool for drug-preformulation studies providing the pharmacotechnical data required when formulating a drug in tablet form. In addition, the results were effective for defining the most appropriate manufacturing technology.


*Keywords:* Expert system; Preformulation; Formulation; Bulk density (Da); Tapped density (Dc); Inter-particle porosity (Ie); Angle of repose ($\alpha$); Flowability ($t''$); Particle size (%Pf); Direct compression (DC)

## 1. Introduction

The SeDeM Method [1] is a new galenic method for application to tablet-preformulation studies. It provides information about the suitability of active ingredients or excipients in powder for direct compression. This information indicates the degree to which the substance can be successfully compressed by means of direct-compression technology. The SeDeM Method allows to detect the powder properties that need to be adjusted to facilitate the formulation of the end product for direct-compression. The SeDeM Diagram also provides an guide for an active ingredient's most appropriate form for oral administration. The obtained data allow to select the most suitable of the commonly used oral forms (tablets, capsules, solutions and suspensions). Rejection of the less appropriate forms according to the characteristics of the active ingredient or excipient under study is also provided.

Because objective parameters are under study, the characterization of a powdered substance should be reproducible, when applied to the production method. The SeDeM Method is, therefore, also a useful tool for studying the reproducibility of the process used for preparing a powder substance and, consequently, for its validation. A single production process can give rise to logical variations in the end product, but these variations should always be within the established limits or specifications. The purpose of the study carried out was to verify the applicability of the SeDeM Method to ascertain the batch-to-batch

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reproducibility of any given API, and to establish the appropriate specifications for the different characterization parameters that would ensure a reproducible quality, regardless of the batch. These specifications should also be used to set an acceptable range for each parameter adopted in accordance with the SeDeM Method, with the aim of providing valid specifications for any powder substance regarding its suitability for direct compression.

The selected parameters of the SeDeM Diagram are consequently studied and analysed statistically, as necessary, to verify the potential equivalence between batches. Once such equivalence is found, it is possible to establish the operating range for each characterization parameter in order to ensure the galenic suitability of the powder substance. Accordingly, batch-to-batch reproducibility would ensure that the quality of the tablets obtained with the API in question is also reproducible, regardless of the batch used.

## 2. Product characterization using the SeDeM Method

As established in an earlier paper [1], the SeDeM Method is based on the experimental study and quantitative determination of the characterization parameters of powdered substances that provide the necessary information about substance's appropriateness for obtaining tablets by direct-compression technology. The considered parameters are as follows:

- Bulk density (Da)
- Tapped density (Dc)
- Inter-particle porosity (Ie)
- Carr index (IC)
- Cohesion index (Icd)
- Hausner ratio (IH)
- Angle of repose ($\alpha$)
- Flowability ($t''$)
- Loss on drying (%HR)
- Hygroscopicity (%H)
- Particle size (%Pf)
- Homogeneity index (I$\theta$)

These parameters are determined by means of the new SeDeM Diagram method, based on known Eq. (1) and duly validated and reproducible experimental tests, as shown in Table 1.

## 3. Materials and methods

The material under study was glucosamine salt F0130, an API of natural origin used in the treatment of rheumatic and arthritic disorders and administered in the form of tablets, capsules, solutions and suspensions. Batches 4/0008, 4/0009 and 4/0011 from the manufacturer, Bioiberica S.A., were studied.

The procedure for the galenic characterization of this substance required the parameters of the SeDeM Diagram to be determined [1]. Whenever possible, the methods indicated in pharmacopoeias were applied. If not available, a system based on the usual practice in galenic research was proposed, adapted specifically for the SeDeM Diagram [1].

- *Bulk density (Da):* In accordance with the method described in Section 2.9.15 of Eur. Ph. [2]
- *Tapped density (Dc)*: According to the method described in Section 2.9.15 of Eur. Ph. [2]. The volume taken is the value obtained after 2500 strokes using a settling apparatus with a graduated cylinder (voluminometer).
- *Inter-particle porosity (Ie)*: This is the inter-particle porosity of the powder mixture [3] and is calculated by the following equation:

$$\mathrm{Ie} = \mathrm{Dc} - \mathrm{Da}/\mathrm{Dc} \times \mathrm{Da} \quad (1)$$

- *Carr index (IC%)* [4–8]: This is calculated from Da and Dc as:

$$\mathrm{IC} = (\mathrm{Dc} - \mathrm{Da}/\mathrm{Dc})100 \quad (2)$$

- *Cohesion index (Icd)*: The cohesion index is determined by directly compressing the product under study. An eccentric press is recommended. Determine the hardness ($N$) of the tablets obtained. Calculate the mean hardness obtained. Test initially with the powder by itself, but if abrasive (cannot be compressed), 3.5% of the following standard lubricant mixture should be added:

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

- *Hausner ratio (IH)* [4]: This is calculated from Da and Dc as:

$$\mathrm{IH} = \mathrm{Dc}/\mathrm{Da} \quad (3)$$

- *Angle of repose ($\alpha$)* [5,9]: This is the angle of the cone formed when the product is passed through a funnel with the following dimensions: funnel height 9.5 cm, upper diameter of spout 7.2 cm, internal diameter at the bottom, narrow end of spout 1.8 cm. Place the funnel on a support at 20 cm from table surface, centred over a millimetre-grid sheet on which two intersecting lines are drawn, crossing at the centre. Plug the narrow end of the funnel spout and fill the funnel with the product under study 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 radius of the cone base with a slide calliper and calculate the mean value ($r$). Measure the cone height ($h$). Calculate the angle tangent value ($\alpha$) of the cone by using the following equation:

$$\mathrm{tg}(\alpha) = h/r \quad (4)$$

Deduct $\alpha$ from the tangent value.

Table 1
Parameters and equations used in SeDeM methodology

| Incidence | Parameter | Symbol | Unit | Equation |
|---|---|---|---|---|
| Dimension | Bulk density | Da | g/ml | $Da = P/V_a$ |
| | Tapped density | Dc | g/ml | $Dc = P/V_c$ |
| Compressibility | Inter-particle Porosity | Ie | – | $Ie = Dc - Da/Dc \times Da$ |
| | Carr index | IC | % | $IC = (Dc - Da/Dc)100$ |
| | Cohesion index[a] | Icd | N | (Experimental) |
| Flowability/powder flow | Hausner ratio | IH | – | $IH = Dc/Da$ |
| | Angle of repose | (α) | ° | $tg\alpha = h/r$ |
| | Powder flow | $t''$ | s | Experimental |
| Lubricity/stability | Loss on drying | %HR | % | Experimental |
| | Higroscopicity | %H | % | Experimental |
| Lubricity/dosage | Particles < 50 μ | %Pf | % | Experimental |
| | Homogenity index[b] | (Iθ) | – | $I\theta = F_m/100 + \Delta F_{mn}$[a] |

[a] Hardness ($N$) of the tablets obtained with the product in question, alone or blended with lubricants if highly abrasive.
[b] Determine particle size. In accordance with the percentages of the different particle-size fractions, applying Eq. (5).

- *Flowability* ($t''$): In accordance with the method described in Section 2.9.16-2 of Eur. Ph. [10]. It is expressed in seconds and tenths of a second per 100 grams of sample, with the mean value of three determinations always being taken.
- *Loss on drying (%HR)*: This is determined by the loss-on-drying test carried out in accordance with General method 2.2.32 in Eur. Ph. [11]. Dry in an oven at 105 °C ± 2 °C, until a constant weight is obtained.
- *Hygroscopicity (%H)*: Determination of the sample weight increase after being kept in a humidifier at ambient relative humidity of 76% (±2%) and a temperature of 22 °C ± 2 °C for 24 h.
- *Percentage of particles measuring <50 μ (%Pf)*: Particle size is determined by means of the sieve test in accordance with the General method 2.9.12 of Eur. Ph. [12]. Determine the % of particles that pass through a 0.05 mm sieve when vibrated for 10 min at speed 10 (CISA vibrator).
- *Homogeneity index (Iθ)*: In accordance with the general method described in General method 2.9.12 of Eur. Ph. [12] for determining particle size by means of the sieve test, the grain size of a 100 g sample is determined by submitting a sieve stack to vibration for 10 min at speed 10 (CISA vibrator). Sieve sizes used: 0.355 mm, 0.212 mm, 0.100 mm and 0.05 mm. Calculate the percentage of product retained in each sieve and the quantity that passes through the 0.05 mm sieve. The percentage of fine particles (<50 μ) that will be considered is determined previously in a separate operation. It should be borne in mind that if this percentage is higher to the complete sieve test is because some of the particles may become adhered to the product retained in the different sieves when doing the grain-size test, and the percentage of <50 μ particles found may be lower than the real figure.

The following equation is then applied to the data obtained.

$$I\theta = F_m/100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + (d_{m+2} - d_m)F_{m-2} + \cdots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}, \quad (5)$$

where Iθ, Relative homogeneity index. Particle-size homogeneity in the range of the fractions under study; $F_m$, percentage of particles in the majority range; $F_{m-1}$, percentage of particles in the range immediately below the majority range; $F_{m+1}$, 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 majority fraction; $d_m$, mean diameter of the particles in the majority fraction; $d_{m-1}$, mean diameter of the particles in the fraction of the range immediately below the majority range; $d_{m+1}$, mean diameter of the particles in the fraction of the range immediately above the majority range.

Once the values have been obtained following the specific methods, certain limits are set based on the study of the chosen parameters and the values described in the Handbook of Pharmaceutical Excipients [13]. See Table 2.

The next step is to convert the numeric limits for each SeDeM Diagram parameter to radius values $r$, in accordance with Table 3 [1] .

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 of the parameters that determine whether or not the product is suitable for direct compression. In this case, the SeDeM Diagram is made up of 12 parameters, which would form an irregular 12-sided polygon (Fig. 1).

To determine whether or not the product is acceptable for direct compression in numerical form, the following indexes are calculated based on the SeDeM Diagram as:

$$\text{Parameter index (IP)} \quad IP = \frac{\text{No. } p \geqslant 5}{\text{No. Pt}} \quad (6)$$

Table 2
Limit values accepted for the SeDeM Diagram parameters

| Incidence | Parameter | Acceptable range |
|---|---|---|
| Dimension | Bulk density | 0–1 g/ml |
| | Tapped density | |
| Compressibility | Inter-particle porosity | 0–1.2 |
| | Carr index | 0–50 (%) |
| | Cohesion index | 0–200 (*N*) |
| Flowability/powder flow | Hausner ratio | 3–0 |
| | Angle of repose | 50–0 (°) |
| | Powder flow | 20–0 (s) |
| Lubricity/stability | Loss on drying | 0–1–2–3…10 (%) |
| | Higroscopicity | 20–0 (%) |
| Lubricity/dosage | Particles < 50 μ | 50–0 (%) |
| | Homogeneity index | $0–2\times10^{-2}$ |

No. $p \geqslant 5$: 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:

$IP \geqslant 0.5$

Parameter profile index (IPP) IPP = mean $r$ of all parameters

Mean $r$ = mean value of the parameters calculated.

The acceptability limit would correspond to:

$IPP = \text{mean } r \geqslant 5$

Good compression index (IGC) is calculated as follows:

$$\textit{Good compression index } (IGC) IGC = IPP \times f \quad (7)$$

Where $f$ is a reliability factor and is calculated as follows:

$$f = \frac{\text{Polygon area}}{\text{Circle area}} \quad (8)$$

The acceptability limit will be calculated by:

$$IGC = IPP \times f \geqslant 5 \quad (9)$$

## 4. Results and discussions

The parameter values were obtained in accordance with the described methodology. Each of the Diagram radius was calculated by applying the equations in Table 1, converting the values obtained into radius ($r$) as described in Table 3.

Each parameter was determined three times and the mean value used for radius calculation.

The corresponding parameters and the radius mean values obtained with samples of batches 4/0008, 4/0009 and 4/0011 are shown in Tables 5–7.

Table 3
Conversion of limits for each parameter into radius values ($r$)

| Incidence | Parameter | Limit value | 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 | $v/5$ |
| | Cohension index | 0–200 | 0–10 | $v/20$ |
| Flowability/powder flow | Hausner ratio | 3–0 | 0–10 | $10-(10v/3)$ |
| | Angle of repose | 50–0 | 0–10 | $10-(v/5)$ |
| | Powder flow | 20–0 | 0–10 | $10-(v/2)$ |
| Lubricity/estability | Loss on drying[a] | 0–1–**2**–3–10 | 0–5–**10**–0 | [b] |
| | Higroscopicity | 20–0 | 0–10 | $10-(v/2)$ |
| Lubricity/dosage | Particles < 50 μ | 50–0 | 0–10 | $10-(v/5)$ |
| | Homogeneity index | $0–2\times10^{-2}$ | 0–10 | $500v$ |

[a,b] Calculate $r$ for the "Loss on drying" parameter as indicated in Table 4, in accordance with the value obtained and as described in the previous paper on the subject [1].

Table 4
Calculation of $r$, based on the loss on drying value

| | | Description | Range (a) | Range (b) | Range (c) |
|---|---|---|---|---|---|
| Range of values | | Range value intervale | 0 a 2 | 3 a 10 | 2 a 3 |
| | | Radius ($r$) range to apply | 0 a 10 | 5 a 0 | 10 a 0 |
| Symbol | $R_{max}$ | Radius top value | 10 | 5 | 10 |
| | $V_{max}$ | Range top value | 2 | 10 | 4 |
| | $V_{min}$ | Range minimum value | 0 | 3 | 2 |
| | $V$ | Experimental value | $V$ | $V$ | $V$ |
| Equations | | $r$ = Radius value calculated | $r=(R_{max}V)/(V_{max})$ | $r=(R_{max}(V_{max}-V))/(V_{max}-V_{min})$ | |

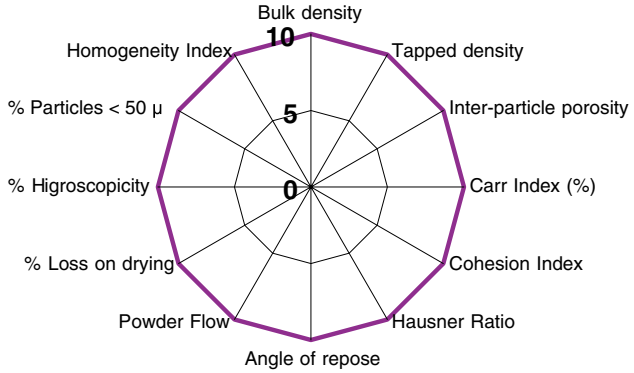


Fig. 1. Diagram SeDeM.

The SeDeM Diagrams with the results of the mean radii of the three values for each batch are shown in Figs. 2–4, respectively.

The test results obtained were treated statistically using Statgraphics 5.1, in order to verify the possible equivalence between the three batches of API studied. Table 8 shows the mean ($\bar{X}$), the variance ($S^2$), the standard deviation of the mean ($S_{n-1}$) and the coefficient of variation (CV%) for each parameter and the IGC, calculated for $n-1$ elements.

The average of the overall means for each batch was calculated based on the data in Table 8, together with the variance ($S^2$), standard deviation for $n-1$ elements ($S_{n-1}$) and the coefficient of variation (CV%). These values are shown in Table 9.

Table 5
Test results for glucosamine salt batch 4/0008

| Incidence | Parameter | Symbol | Unit | $V1$ | $V2$ | $V3$ | $\bar{V}$ | $R1$ | $R2$ | $R3$ | $\bar{R}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dimensions | Bulk density | Da | g/ml | 0.790 | 0.805 | 0.839 | 0.811 | 7.90 | 8.05 | 8.39 | 8.11 |
| | Tapped density | Dc | g/ml | 1.127 | 1.127 | 1.193 | 1.149 | 11.27 | 11.27 | 11.93 | 11.49 |
| Compressibility | Inter-particle porosity | Ie | – | 0.379 | 0.355 | 0.354 | 0.362 | 3.15 | 2.96 | 2.95 | 3.02 |
| | Carr Index | IC | % | 29.902 | 28.571 | 29.673 | 29.382 | 5.98 | 5.71 | 5.93 | 5.87 |
| | Cohesion Index | Icd | N | 0.000 | 0.000 | 0.000 | 0.000 | 0.00 | 0.00 | 0.00 | 0.00 |
| Flowability/powder flow | Hausner Ratio | IH | – | 1.427 | 1.400 | 1.422 | 1.416 | 5.24 | 5.33 | 5.26 | 5.28 |
| | Angle of repose | (α) | ° | 30.450 | 33.680 | 29.890 | 31.340 | 3.91 | 3.26 | 4.02 | 3.73 |
| | Powder flow | $t''$ | s | 1.000 | 1.000 | 1.000 | 1.000 | 9.50 | 9.50 | 9.50 | 9.50 |
| Lubrication/stability | Loss on drying | %HR | % | 0.140 | 0.120 | 0.180 | 0.147 | 0.70 | 0.60 | 0.90 | 0.73 |
| | Higroscopicity | %H | % | 0.070 | 0.340 | 0.520 | 0.310 | 9.97 | 9.83 | 9.74 | 9.85 |
| Dosage/lubrication | Particles < 50 μ | %Pf | μ | 12.000 | 13.000 | 12.000 | 12.333 | 7.60 | 7.40 | 7.60 | 7.53 |
| | Homogenity Index | (Iθ) | | 0.0019 | 0.0025 | 0.0020 | 0.002 | 0.95 | 1.25 | 1.00 | 1.07 |
| | | | | Parametric index | | | | 0.58 | 0.58 | 0.58 | 0.58 |
| | | | | Parametric profile (radius mean) | | | | 5.51 | 5.43 | 5.60 | 5.52 |
| | | | | Good compression index (IGC) | | | | 5.25 | 5.17 | 5.33 | 5.25 |

Table 6
Test results for glucosamine salt batch 4/0009

| Incidence | Parameter | Symbol | Unit | $V1$ | $V2$ | $V3$ | $\bar{V}$ | $R1$ | $R2$ | $R3$ | $\bar{R}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dimensions | Bulk density | Da | g/ml | 0.824 | 0.806 | 0.827 | 0.819 | 8.24 | 8.06 | 8.27 | 8.19 |
| | Tapped density | Dc | g/ml | 1.162 | 1.158 | 1.140 | 11.53 | 11.62 | 11.58 | 11.40 | 11.53 |
| Compressibility | Inter-particle porosity | Ie | – | 0.353 | 0.377 | 0.332 | 0.354 | 2.94 | 3.14 | 2.77 | 2.95 |
| | Carr index | IC | % | 29.088 | 30.397 | 27.456 | 28.980 | 5.82 | 6.08 | 5.49 | 5.80 |
| | Cohesion index | Icd | N | 0.000 | 0.000 | 0.000 | 0.000 | 0.00 | 0.00 | 0.00 | 0.00 |
| Flowability/powder flow | Hausner ratio | IH | – | 1.410 | 1.437 | 1.378 | 1.408 | 5.30 | 5.21 | 5.41 | 5.31 |
| | Angle of repose | (α) | ° | 29.860 | 33.370 | 29.030 | 30.753 | 4.03 | 3.33 | 4.19 | 3.85 |
| | Powder flow | $t''$ | s | 1.000 | 1.000 | 1.000 | 1.000 | 9.50 | 9.50 | 9.50 | 9.50 |
| Lubrication/stability | Loss on drying | %HR | % | 0.170 | 0.160 | 0.110 | 0.147 | 0.85 | 0.80 | 0.55 | 0.73 |
| | Higroscopicity | %H | % | 0.000 | 0.210 | 0.110 | 0.107 | 10.00 | 9.90 | 9.95 | 9.95 |
| Dosage/lubrication | Particles < 50 μ | %Pf | μ | 13.000 | 13.000 | 12.000 | 12.667 | 7.40 | 7.40 | 7.60 | 7.47 |
| | Homogenity Index | (Iθ) | | 0.0023 | 0.0025 | 0.0029 | 0.003 | 1.15 | 1.25 | 1.45 | 1.28 |
| | | | | Parametric index | | | | 0.58 | 0.58 | 0.58 | 0.58 |
| | | | | Parametric profile (radius mean) | | | | 5.57 | 5.52 | 5.55 | 5.55 |
| | | | | Good compression index (IGC) | | | | 5.30 | 5.26 | 5.28 | 5.28 |

Table 7
Test results for glucosamine salt batch 4/0011

| Incidence | Parameter | Symbol | Unit | $V1$ | $V2$ | $V3$ | $\bar{V}$ | $R1$ | $R2$ | $R3$ | $\bar{R}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dimensions | Bulk density | Da | g/ml | 0.809 | 0.807 | 0.827 | 0.814 | 8.09 | 8.07 | 8.27 | 8.14 |
| | Tapped density | Dc | g/ml | 1.161 | 1.158 | 1.140 | 1.153 | 11.61 | 11.58 | 11.40 | 11.53 |
| Compressibility | Inter-particle porosity | Ie | – | 0.375 | 0.376 | 0.332 | 0.361 | 3.12 | 3.13 | 2.77 | 3.01 |
| | Carr index | IC | % | 30.319 | 30.311 | 27.456 | 29.362 | 6.06 | 6.06 | 5.49 | 5.87 |
| | Cohesion index | Icd | N | 0.000 | 0.000 | 0.000 | 0.000 | 0.00 | 0.00 | 0.00 | 0.00 |
| Flowability/powder flow | Hausner ratio | IH | – | 1.435 | 1.435 | 1.378 | 1.416 | 5.22 | 5.22 | 5.41 | 5.28 |
| | Angle of repose | (α) | ° | 29.150 | 30.210 | 29.030 | 29.463 | 4.17 | 3.96 | 4.19 | 4.11 |
| | Powder flow | $t''$ | s | 1.000 | 1.000 | 1.000 | 1.000 | 9.50 | 9.50 | 9.50 | 9.50 |
| Lubrication/stability | Loss on drying | %HR | % | 0.134 | 0.100 | 0.180 | 0.138 | 0.67 | 0.50 | 0.90 | 0.69 |
| | Higroscopicity | %H | % | 0.000 | 0.020 | 0.000 | 0.007 | 10.00 | 9.97 | 10.00 | 9.99 |
| Dosage/lubrication | Particles < 50 μ | % Pf | μ | 13.000 | 12.000 | 11.000 | 12.000 | 7.40 | 7.60 | 7.80 | 7.60 |
| | Homogenity index | (Iθ) | | 0.0027 | 0.0029 | 0.0028 | 0.003 | 1.35 | 1.45 | 1.40 | 1.40 |
| | | | | Parametric index | | | | 0.58 | 0.58 | 0.58 | 0.58 |
| | | | | Parametric profile (radius mean) | | | | 5.60 | 5.59 | 5.59 | 5.59 |
| | | | | Good compression index (IGC) | | | | 5.33 | 5.32 | 5.33 | 5.32 |

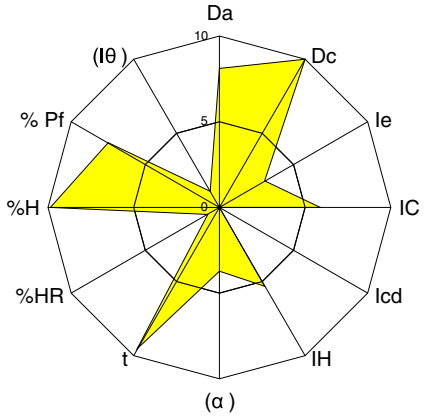


Fig. 2. SeDeM Diagram for glucosamine salt batch 4/0008.

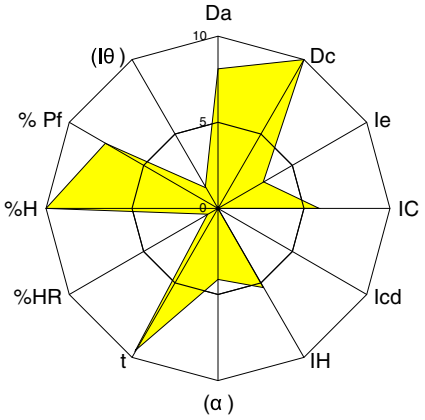


Fig. 4. SeDeM Diagram for glucosamine salt batch 4/0011.

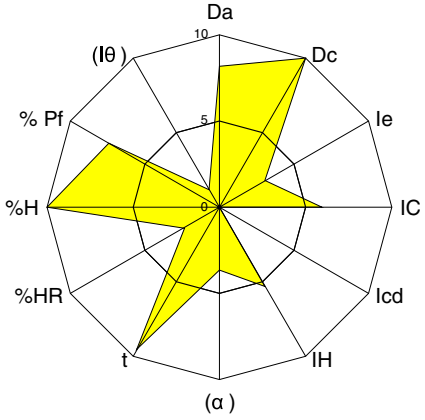


Fig. 3. SeDeM Diagram for glucosamine salt batch 4/0009.

The possibility of applying parametric statistics by means of the Cochran, Bartlett and Hartley tests was first verified, as well as the asymmetry or Pearson's test and the Kurtosis test. A one-way analysis of variance (ANOVA) was used for the statistical study of each parameter to which parametric statistics could be applied. The Kruskal–Wallis analysis was applied to the other parameters. The results of the tests carried out are shown in Table 10.

The statistical analyses performed to determine the kind of statistics (parametric or non-parametric) to be applied in each case showed that parametric statistics can be used for all the parameters under study except for IGC, because this is the only parameter for which statistically significant differences are obtained with a probability level of 5% ($p > 0.05$) for the Cochran and Bartlett tests.

Statistical significance analysis shows that no statistically significant differences ($p > 0.05$) exist between the three batches for any of the parameters studied. That is all three batches of the glucosamine salt F0130 presented equivalent characteristics in terms of their galenic properties and suitability for direct compression. This indicates that the glucosamine salt F0130 process has good reproducibility and reliability and generates batches that have equivalent pharmacotechnical properties for the parameters included in the present study.

Table 8
Statistical parameters for each batch of glucosamine salt

| Parameter | Batch 4/0008 | | | | Batch 4/0009 | | | | Batch 4/0011 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $\overline{X}$ | $S^2$ | $S_{n-1}$ | CV% | $\overline{X}$ | $S^2$ | $S_{n-1}$ | CV% | $\overline{X}$ | $S^2$ | $S_{n-1}$ | CV% |
| DA | 8.1133 | 0.0630 | 0.2511 | 3.0945 | 8.1900 | 0.0129 | 0.1136 | 1.3868 | 8.1433 | 0.0121 | 0.1102 | 1.3527 |
| Dc | 11.4500 | 0.1452 | 0.3811 | 3.3280 | 11.5333 | 0.0137 | 0.1172 | 1.0161 | 11.5300 | 0.0129 | 0.1136 | 0.9851 |
| Ie | 3.0200 | 0.0127 | 0.1127 | 3.7316 | 2.9500 | 0.0343 | 0.1852 | 6.2781 | 3.0067 | 0.0420 | 0.2050 | 6.8188 |
| IC | 5.8733 | 0.0206 | 0.1436 | 2.4457 | 5.7967 | 0.0874 | 0.2957 | 5.1010 | 5.8700 | 0.1083 | 0.3291 | 5.6063 |
| Icd[a] | | | | | | | | | | | | |
| IH | 5.1767 | 0.0022 | 0.0473 | 0.9129 | 5.3067 | 0.0100 | 0.1002 | 1.8876 | 5.2833 | 0.0120 | 0.1097 | 2.0763 |
| α | 3.7300 | 0.1687 | 0.4107 | 11.0116 | 3.8500 | 0.2092 | 0.4574 | 11.8801 | 4.1067 | 0.0162 | 0.1274 | 3.1025 |
| $t''$[a] | | | | | | | | | | | | |
| %HR | 0.7333 | 0.0233 | 0.1528 | 20.8300 | 0.7333 | 0.0258 | 0.1607 | 21.9175 | 0.6900 | 0.0403 | 0.2007 | 29.0941 |
| %H | 9.8467 | 0.0134 | 0.1159 | 1.1771 | 9.9500 | 0.0025 | 0.0500 | 0.5025 | 9.9900 | 0.0003 | 0.0173 | 0.1734 |
| %Pf | 7.5333 | 0.0133 | 0.1155 | 1.5328 | 7.4667 | 0.0133 | 0.1155 | 1.5465 | 7.6000 | 0.0400 | 0.2000 | 2.6316 |
| Iθ | 1.0667 | 0.0258 | 0.1607 | 15.0682 | 1.2833 | 0.0233 | 0.1528 | 11.9029 | 1.4000 | 0.0025 | 0.0500 | 3.5714 |
| IGC | 5.2500 | 0.0064 | 0.0003 | 0.0063 | 5.2800 | 0.0004 | 0.0200 | 0.3788 | 5.3267 | 0.0000 | 0.0058 | 0.1084 |

[a] All values for both parameters were found to be the same. So they could not be analysed statistically.

Table 9
Mean statistical parameters of the three batches of glucosamine salt studied

| Parameter | Mean | | | |
|---|---|---|---|---|
| | $\overline{X}$ | $S^2$ | $S_{n-1}$ | CV% |
| DA | 8.1489 | 0.0294 | 0.1583 | 1.9446 |
| Dc | 11.5044 | 0.0573 | 0.2039 | 1.7764 |
| Ie | 2.9922 | 0.0297 | 0.1676 | 5.6095 |
| IC | 5.8467 | 0.0721 | 0.2561 | 4.3843 |
| Icd[a] | | | | |
| IH | 5.2556 | 0.0081 | 0.0857 | 1.6256 |
| α | 3.8956 | 0.1314 | 0.3318 | 8.6647 |
| $t''$[a] | | | | |
| %HR | 0.7189 | 0.0298 | 0.1714 | 23.9472 |
| %H | 9.9289 | 0.0054 | 0.0611 | 0.6177 |
| %Pf | 7.5333 | 0.0222 | 0.1436 | 1.9036 |
| Iθ | 1.2500 | 0.0172 | 0.1212 | 10.1808 |
| IGC | 5.2856 | 0.0023 | 0.0087 | 0.1645 |

[a] All values for both parameters were found to be the same. So they could not be analysed statistically.

Table 10
Tests carried out on samples studied

| Parameters | Variance check ($p$-value) | | ANOVA | | |
|---|---|---|---|---|---|
| | Cochran's | Bartlett's | $F$-ratio | $p$-value | Significance |
| DA | 0.2424 | 0.4628 | 0.1500 | 0.8618 | NS |
| Dc | 0.0721 | 0.1965 | 0.0300 | 0.9702 | NS |
| Ie | 0.8360 | 0.7473 | 0.1400 | 0.8724 | NS |
| IC | 0.7484 | 0.5864 | 0.0800 | 0.9258 | NS |
| Icd | – | – | – | | – |
| IH | 0.7645 | 0.5740 | 0.0900 | 0.9134 | NS |
| α | 0.6605 | 0.3245 | 0.8500 | 0.4748 | NS |
| $t''$ | – | – | – | – | |
| %HR | 0.9060 | 0.9306 | 0.0600 | 0.9396 | NS |
| %H | 0.0893 | 0.1049 | 3.0300 | 0.1230 | NS |
| %Pf | 0.4800 | 0.7012 | 0.6000 | 0.5787 | NS |
| Iθ | 0.7500 | 0.3683 | 4.9800 | 0.0531 | NS |
| | Variance check ($p$-value) | | | Kruskal–Wallis | |
| | Cochran's | Bartlett's | | $p$-value | Significance |
| IGC | 0.0121 | 0.0177 | | 0.1825 | NS |

Furthermore, it was demonstrated that the new galenic preformulation method called SeDeM Diagram for characterizing substances in terms of their direct-compression feasibility is also a useful, effective tool for checking the accurate reproducibility of different batches of the same substance, and can consequently be used to validate (under prospective, concurrent and retrospective validation approaches) the manufacturing systems of APIs and excipients for pharmaceutical use.

The results obtained with the three batches of the same API demonstrate that the new method proposed is capable of producing sufficiently reliable and reproducible values. Thus this allows establishing some specifications or limits for each of the parameters used in the SeDeM Diagram, based on the test values obtained and the statistical study of the confidence interval for each parameter. Table 11 shows the lower and upper confidence interval for each parameter with probability levels of 95% and 99% in absolute values and their conversion into percentages with respect to the mean radius (±% confidence interval). Based on the latter figure, the absolute value of each percentage with respect to the same mean value can be calculated (± tolerance units). Except for the IGC parameter, a mean value of 0.433 is obtained for all parameters at a probability level of 95%, and 0.977 at a probability level of 99%. Based on the individual results obtained for each batch studied and for each parameter, a specification of ±1.0 radius unit would seem to be correct for all parameters, given that there is a 100% probability for 7 out of the 10 parameters, and a 97% probability for the other 3 that all individual results obtained would fall within the interval of the established specification, which is sufficiently reasonable, depending on the type of each parameter. Concerning IGC, it would be reasonable to set a narrower limit given that this parameter combines all the parameters studied in one overall value; this is also evident from the

Table 11
Tolerance units based on the confidence interval for each parameter

| Parameter | Radius mean | (%) Probability level | Confidence intervals | ±% confidence | Tolerance units (±) |
|---|---|---|---|---|---|
| DA | 8.14 | 95 | 7.76–8.54 | 4.79 | 0.39 |
| | | 99 | 7.24–9.06 | 11.18 | 0.91 |
| DC | 11.52 | 95 | 11.01–12.02 | 4.38 | 0.51 |
| | | 99 | 10.26–12.69 | 10.55 | 1.22 |
| Ie | 2.99 | 95 | 2.58–3.41 | 13.88 | 0.42 |
| | | 99 | 2.03–3.95 | 32.11 | 0.96 |
| IC | 5.84 | 95 | 5.21–6.48 | 10.87 | 0.64 |
| | | 99 | 4.38–7.31 | 25.09 | 1.47 |
| IH | 5.29 | 95 | 5.07–5.50 | 4.06 | 0.22 |
| | | 99 | 4.80–5.78 | 10.11 | 0.54 |
| α | 3.9 | 95 | 3.07–4.72 | 21.15 | 0.83 |
| | | 99 | 1.99–5.8 | 48.85 | 1.91 |
| %HR | 0.72 | 95 | 0.29–1.15 | 59.72 | 0.43 |
| | | 99 | 0.26–1.70 | 100.00 | 0.72 |
| %H | 9.93 | 95 | 9.78–10.08 | 1.51 | 0.15 |
| | | 99 | 9.58–10.28 | 3.58 | 0.36 |
| %Pf | 7.58 | 95 | 7.15–8.00 | 5.61 | 0.43 |
| | | 99 | 6.59–8.56 | 12.99 | 0.99 |
| Iθ | 1.22 | 95 | 0.94–1.55 | 25.00 | 0.31 |
| | | 99 | 0.56–1.94 | 56.56 | 0.69 |
| Icd | 0 | 95 | 0–0 | – | – |
| | | 99 | 0–0 | – | – |
| $t''$ | 9.5 | 95 | 9.5–9.5 | – | – |
| | | 99 | 9.5–9.5 | – | – |
| IGC | 5.25 | 95 | 5.20–5.37 | 1.62 | 0.09 |
| | | 99 | 5.08–5.49 | 3.90 | 0.21 |

calculations of the confidence interval at 95% (0.09) and at 99% (0.21) probability. In this case, therefore, it is proposed establishing limits of ±0.5 radius unit with respect to the mean value obtained in the experiment.

## 5. Considerations on the feasibility of glucosamine salt F0130 for direct compression

According to the results of the statistical study, the SeDeM Diagram may be considered valid for studying the suitability of a product for direct compression.

In this case, based on the results of the SeDeM Diagram, although the parametric profile was >5 [1] for all three batches of Bioiberica S.A. glucosamine salt F0130 studied, it was not suitable for direct compression, as five of the fundamental parameters (Table 12) were under 5, indicating poor direct compressibility characteristics for the substance.

The results gave mean values of less than 5 for the interparticle porosity and cohesion indices, which means that the characteristics of glucosamine salt F0130 in terms of *compressibility* are negative. Furthermore, homogeneity index values (deriving from the angle of repose and loss on drying) under 5 were obtained, which would have negative effects on product *dosage*. Accordingly, both factors would need to be corrected, based on the corresponding parameters, by adding appropriate excipients that would help to compress these batches of glucosamine salt F0130 directly, or using other technologies.

Table 12
Mean results of each batch of glucosamine salt

| Parameter/batch | 4/0008 | 4/0009 | 4/0011 |
|---|---|---|---|
| Inter-particle Porosity (Ie) | 3.02 | 2.95 | 3.01 |
| Cohesion Index (Icd) | 0.00 | 0.00 | 0.00 |
| Angle of repose (α) | 3.73 | 3.85 | 4.11 |
| Loss on drying (%HR) | 0.73 | 0.73 | 0.69 |
| Homogeneity index (Iθ) | 1.07 | 1.28 | 1.40 |

## 6. Conclusions

1. The SeDeM Diagram is a useful, effective and accurate tool for checking the properties' consistency of different batches of a substance, and can consequently be used to validate (prospective, recurrent and retrospective validation approaches) the manufacturing processes of APIs and excipients for pharmaceutical use.
2. The method provides reliable and reproducible results for the galenic characterization of substances (APIs or excipients) with respect to their suitability for direct compression.
3. A specification of ±1.0 radius units has been established for all SeDeM Diagram parameters except IGC, for which a specification of ±0.5 radius units is proposed.
4. The process by means of which glucosamine salt F0130 is obtained presents good reproducibility and reliability, and generates batches that are equivalent to each other, regarding the pharmacotechnical parameters studied are concerned.
5. The glucosamine salt F0130 made by Bioiberica S.A. and tested in this study has not the appropriate characteristics for direct compression without an excipient. For direct compression of this product, its profile should be corrected by adding suitable excipients. Otherwise, alternative compression technologies should be sought.

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