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Research paper

Optimization of parameters of the SeDeM Diagram Expert System: Hausner index (IH) and relative humidity (%RH)

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ABSTRACT

As a methodology for characterizing substances in relation to their viability in direct compression, the SeDeM Diagram Expert System may be considered an open system in terms of the number of parameters applied and the optimization of these parameters. With the experience acquired from applying the SeDeM Diagram, in this study, we propose optimizing the parameters corresponding to the Hausner index (IH) and relative humidity (%HR) in order to simplify the mathematical calculation, so that it provides reliable data that can be extrapolated. The proposed optimization does not involve a conceptual change in the parameters considered nor a significant change in the results obtained compared with the previous calculation methodology initially established for the SeDeM Diagram Expert System, which means that the conclusions obtained by applying this method are equivalent.

1. Introduction

The SeDeM Method [1] is a new Galenic method for application in tablet-preformulation studies. It provides information about the suitability of active ingredients and excipients in powder for direct compression. This information indicates the degree to which the substances can be successfully compressed by means of direct-compression technology. The SeDeM Method makes it possible to detect the powder properties that need to be adjusted to facilitate the formulation of the end product for direct compression. The SeDeM Method is therefore also a useful tool for studying the reproducibility of the process used to prepare a powder substance and, consequently, for its validation [2]. Furthermore, it has been shown to be a suitable tool for preformulation and formulation by characterizing the Galenic properties of excipients in order to define their suitability for direct compression [3,4].

As established in earlier studies [1,2], 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 a substance's appropriateness for obtaining tablets using direct-compression technology. The parameters considered are the following:

- Bulk density (*Da*)
- Tapped density (*Dc*)
- Inter-particle porosity (*Ie*)
- Carr index (*IC*)
- Cohesion index (Icd)
- Hausner index (IH)
- Angle of repose (α)
- Powder flow (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 [1,2].

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$$^{*}\ I\theta = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + (d_{m+2} - d_m)F_{m-2+\cdots+}(d_m - d_{m-n})F_{m-n+}(d_{m+n} - d_m)F_{m+n}} \quad (1)$$

where $I\theta$: 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.

When the parameters of the SeDeM Diagram had been established, we determined the acceptable numerical limit values for each of the 12 study parameters; these values are shown in Table 2.

2. Materials and methods

The material under study consists of 22 excipients for direct compression and 10 APIs, all of which are listed below: Advantose® 100 Batch 4k26 (SPI Pharma SAS, Septemes Les Vallons, France), Avicel® 101 Batch 6410C (FMC, Brusseles, Belgium), Avicel® 112 Batch 9232C (FMC, Brusseles, Belgium), Avicel® 200 Batch M343C (FMC, Brusseles, Belgium), Emcocel® 50M Batch 550600 (JRS PHARMA GGmbH & Co. KG, Rosenberg, Germany), Emcocel® 90M Batch 6109070238 (JRS PHARMA GGmbH & Co. KG, Rosenberg, Germany), Isomalt® 721 Batch LRE 539 (GalenIQ, Menheim, Germany), Kleptose® Batch 774639 (Roquette Freres 62136, Lestrem, France), Kollidon® VA 64 Batch 28-2921 (Basf, Ludwigshafen, Germany), Lactose Fast Flo Batch 8504081961 (Seppic, Paris, France), Ludipres® Batch 1130015/04020026 (Basf, Ludwigshafen, Germany), Lycatab® 190 Batch 775640 (Roquette Freres 62136, Lestrem, France), Microcel® MC 101 Batch 00206 (Blanver, Farmoquímica, Sao Paulo, Brasil), Microcel® MC 102 Batch 19604 (Blanver, Farmoquímica, Sao Paulo, Brasil), Microcel® MC 250 Batch 1202305 (Blanver, Farmoquímica, Sao Paulo, Brasil), Microcelac® 100 Batch 0402 A 4931 (Meggle, Wasserburg, Germany), Pearlitol® 200 SD Batch E165P (Roquette Freres 62136, Lestrem, France), Pharmaburst® C1 Batch 04K111 (SPI Pharma SAS, Septemes Les Vallons, France), Prosolv® HD90 Batch K950044 (JRS PHARMA GGmbH & Co. KG, Rosenberg, Germany), Vivapur® 101 Batch 6610152949 (JRS PHARMA GGmbH & Co. KG, Rosenberg, Germany), Vivapur® 102 Batch 5610264136 (JRS PHARMA GGmbH & Co. KG, Rosenberg, Germany), Vivapur® 12 Batch 6601260202 (JRS PHARMA GGmbH & Co. KG, Rosenberg, Germany), API F0130 Glucosamine ClH 8/004 (Bioibérica S.A., Barcelona, Spain), API PJ-547 Nucleotides (Bioibérica S.A., Barcelona, Spain), API F0491 chondroitin sulfate 100EP 6/0028 (Bioibérica S.A., Barcelona, Spain), API F0168 Glucosamine sodium sulfate 6/0013 (Bioibérica S.A., Barcelona, Spain), API F0192 Glucosamine potassium sulfate 7/005 (Bioibérica S.A., Barcelona, Spain), API F0324 6/0010 (Bioibérica S.A., Barcelona, Spain), API FT-CS-35 06/90 (Bioibérica S.A., Barcelona, Spain), API FT-CS-35 06/95 (Bioibérica S.A., Barcelona, Spain), API F0349 HYAL-JOINT 5/0026 (Bioibérica S.A., Barcelona, Spain) and API F0380 Chondroitin sodium sulfate JP 6/0012 (Bioibérica S.A., Barcelona, Spain).

Table 2
Accepted limit values for the SeDeM Method parameters.

Incidence	Parameter	Limit values
Dimensions	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 index	3–0
	Angle of repose	50–0 (°)
	Powder flow	20–0 (s)
Lubricity/Stability	Relative humidity	0–1–2–3···10 (%)
	Hygroscopicity	20–0 (%)
Lubricity/Dosage	Particles < 50 μm	50–0 (%)
	Homogeneity index	$0–2 \times 10^{-2}$

The procedure for the Galenic characterization of these substances involves determining the parameters of the SeDeM Diagram [1,2]. The methods indicated in pharmacopoeias were applied wherever possible. Where these methods were not available, we propose a system based on the common practice followed in Galenic research and specifically adapted for the SeDeM Diagram [1,2].

3. Optimization of the calculation of the radius of the Hausner index

In the SeDeM system (see Table 1), one of the parameters determined based on the bulk density (Da) and the tapped density (Dc) obtained by means of volumetric measurement [5] is the Hausner index (IH).

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	%	$IC = (Dc - Da/Dc) \times 100$
	Cohesion index*	Icd	N	Experimental
Flowability/powder flow	Hausner index	IH	–	$IH = Dc/Da$
	Angle of repose	(α)	°	$tg\ \alpha = h/r$
	Powder flow	t''	s	Experimental
Lubricity/stability	Loss on drying	%HR	%	Experimental
	Hygroscopicity	%H	%	Experimental
Lubricity/dosage	Particles < 50 μ	%Pf	%	Experimental
	Homogeneity index**	($I\theta$)	–	$I\theta = Fm/100 + \Delta Fmn$

* Hardness (N) of the tablets obtained with the product in question, alone or blended with lubricants if highly abrasive.
** Determines particle size in accordance with the percentages of the different particle-size fractions by applying Eq. (1).

Formula for the Hausner index:

$$IH = \frac{Dc}{Da}, \quad \text{i.e. } IH = \frac{V_o}{V_f}$$

where V_o, initial volume and V_f, final volume.

To obtain the value for the tapped density, an exact measurement of the volume of compacted powder (V_c) is required; in exceptional cases, the V_c value may be higher than that obtained for the bulk volume (V_a). This is due to a number of factors that affect the spatial distribution of the particles. Following are some of these factors.

(1) *Electrostatic forces*. When the particles interact, giving rise to repulsion phenomena that can affect the volume measurement reached after settling by compacting in the bulk density (*Da*) and tapped density (*Dc*) assays [6].
(2) *Particle size*. The size of the particles is inversely proportional to the cohesion, so this factor can affect the appearance of electrostatic charges (larger surface area and greater friction). In this case, the flow becomes very difficult or nonexistent [6].
(3) *Core flow and mass flow*. The above factors cause the phenomena of core flow and mass flow, which cause the powder to settle, respectively, in the form of a central funnel or a raised central cone.

Other factors that may affect the measurement of the settled powder include the elasticity of the particles and Born repulsion forces [6].

In the SeDeM system [1], the limits for calculating the Hausner index were established based on the experimental study of 22 excipients, the values of which were between 1.1 and 2.46. In order to obtain greater variation and simplicity of calculation, these values were adapted to the current limits of 3 to 0. It was also found that only one of these excipients produced abnormal values, with a tapped volume greater than the bulk volume, due to the fact that when the assay was performed, the powder adhered to the walls (mass-flow factor). In this case, the flow was nonexistent.

As a result of the above study, it was deduced that the calculation of the parameter corresponding to the Hausner index could be optimized by modifying the limit values (currently between 3 and 0) and applying stricter values.

Therefore, for the parameter corresponding to the Hausner index, we propose limit values between 3 and 1 (3 corresponds to a radius of 0 and 1 corresponds to a radius of 10). Exceptional values of less than 1 should be considered values corresponding to nonflowing or almost nonflowing products that would have a radius of zero, as shown in Table 3. For radius calculation is necessary to use the equation 10-(10*V*/3).

4. Optimization of the calculation of the radius of relative humidity (%HR)

We also propose a simplification in the calculation of the value of the radius for the parameter % relative humidity (%HR). The simplification consists of replacing the calculation of the radius of %HR based on its experimental value (which is currently verified using three ranges) with a much simpler linear calculation similar to the calculations applied to the other parameters of the SeDeM Diagram Expert System, as shown in the following formulae:

(A) Current calculation based on three ranges (ranges, 0–2, 3–10 and 2–3) using the experimental value obtained.
- Range (a); range of value = 0–2;

$$R = \frac{(R_{\max})V}{V_{\max}}$$

where $R_{\max}$ = maximum radius = 10; $V_{\max}$ = maximum value = 2; and V = experimental value.
- Range (b); range of value = 3–10;

$$R = \frac{(R_{\max})V_{\max} - V}{(V_{\max} - V_{\min})}$$

where $R_{\max}$ = maximum radius = 5; $V_{\max}$ = maximum value = 10; $V_{\min}$ = minimum value = 3; and V = experimental value.
- Range (c); range of value = 2–3;

$$R = \frac{R_{\max}(V_{\max} - V)}{(V_{\max} - V_{\min})}$$

where $R_{\max}$ = maximum radius = 10; $V_{\max}$ = maximum value = 4; minimum value = 2; and V = experimental value.

(B) Linear calculation: a single range from 10 to 0 (much simpler and applicable optimized calculation).

$$r = 10 - V$$

where V = experimental value.

The initial approach was to calculate the relative humidity parameter based on establishing three ranges because the percentage relationship obtained from the determination of the humidity of the substance analysed did not bear a linear relationship to the correct behaviour of the powder. Humidity below 1% means that the powder is very dry, leading to the generation of an electrostatic charge, which makes it difficult for the powder to flow. Furthermore, low percentages of humidity do not favour the compression of the substance (some humidity between the particles is necessary for compacting). Humidity of over 3% leads to clumping, with the resulting poor flowability, and also favours adhesion to punches and dies. It was therefore deemed that this parameter should be treated differently from the other parameters, as it will present optimum experimental values (between 1% and 3%) [7] and, based on these, it will present progressively poorer values in both directions : below 1% and above 3%. However, the experience consolidated in the use of the SeDeM Diagram has shown that the calculation of the relative humidity parameter can be simplified without significant variations in the results obtained.

This proposal was made after experimentally obtaining the percentage of relative humidity of a number of substances (22 different excipients for direct compression and 10 different APIs) and calculating the corresponding radii of this parameter. Based on these results, the corresponding calculations of the radius are performed using the previous nonlinear system (ranges) and the optimized simple linear system proposed for adoption from now on.

Table 3
Correspondence of experimental values to SeDeM radius.

Values and conversions	Function or incidence	Parameter	Limit values	Conversion to radii (*r*)
Current	Flowability/powder flow	Flowability	3–0	0–10
Proposed	Flowability/powder flow	Flowability	3–1	0–10
	Flowability/powder flow	Flowability	<1	0

Table 4
Comparison of values of radii of %HR calculated by ranges (nonlinear) and calculated linearly.

Excipient	Composition	%HR experimental value	*r* %HR by ranges/ linear	Mean ranges/ linear	%H experimental value	Radius %H	"*L*/*S*" function by ranges/ linear	Mean "*L*/*S*" function by *r* %HR
Advantose 100 Batch 4k26	Crystalline maltose	1.490	7.45	7.98	0.45	9.78	8.61	8.88
			8.51				9.14	
Avicel 101 Batch 6410C	Microcrystalline cellulose	4.620	3.84	4.61	3.36	8.17	6.01	6.40
			5.38				6.78	
Avicel 112 Batch 9232C	Microcrystalline cellulose	3.120	4.91	5.895	7.5	7.5	6.21	6.70
			6.88				7.19	
Avicel 200 Batch M343C	Microcrystalline cellulose	3.350	4.75	5.7	5.07	7.47	6.11	6.59
			6.65				7.06	
Emcocel 90 M Batch 6109070238	Microcrystalline cellulose	5.20	3.43	4.115	3.52	8.12	5.77	6.12
			4.8				6.46	
Emcocel 50 M Batch 550600	Microcrystalline cellulose	5.570	2.79	3.61	1.3	9.35	6.07	6.48
			4.43				6.89	
ISomalt 721 Batch LRE539	Glucopyranosyl/mannitol/sorbitol	4.390	4.01	4.81	9.89	9.89	6.95	7.35
			5.61				7.75	
Kleptose Batch 774639	beta-Cyclodextrin	12.070	0.00	0.00	8.12	8.12	4.06	4.06
			0.00				4.06	
Kollidon VA 64 Batch 28–2921	Copovidone	5.540	3.19	3.825	14.31	2.85	3.02	3.34
			4.46				3.65	
Lactosa Fast Flo Batch 8504081961	Lactose	3.060	4.96	5.95	0.00	10.00	7.48	7.98
			6.94				8.47	
Ludipres Batch 1130015/ 04020026	PVP, crospovidone + lactose	2.560	7.20	7.32	0.74	9.63	8.42	8.48
			7.44				8.54	
Lycatab190 Batch 775640	Calcium carbonate + starch	2.340	8.3	7.98	0.38	9.81	9.06	8.90
			7.66				8.74	
MicrocelMC101 Batch 002/06	Microcrystalline cellulose	6.085	2.80	3.36	7.97	7.97	5.38	5.66
			3.92				5.94	
MicrocelMC102 Batch 1960/4	Microcrystalline cellulose	5.520	3.20	3.84	1.8	9.1	6.15	6.47
			4.48				6.79	
Microcel MC 250 Batch 12023/ 05	Microcrystalline cellulose	5.840	2.97	3.565	3.4	8.48	5.73	6.03
			4.16				6.32	
Microcelac 100 Batch 0402 A 4931	alfa-lactose monohydrate + Mycrocrystalline cellulose	1.720	8.60	8.44	1.43	9.29	8.94	8.86
			8.28				8.78	
Pearlitol 200 SD Batch E165P	Granulated mannitol	*0.340*	*1.7*	*5.68*	*8.53*	*9.84*	*5.77*	*7.76*
			9.66				*9.75*	
Pharmaburst C1 Batch 04K111	Mannitol + St1500 + crosp + croscaram + SI 02	*1.140*	5.7	7.28	6.72	6.72	6.21	7
			8.86				7.79	
Prosolv HD90 Batch K950044	Microcrystalline cellulose + SiO_2	5.190	3.44	4.125	2.29	8.86	6.15	6.49

(*continued on next page*)

Table 4 (*continued*)

Excipient	Composition	%HR experimental value	*r* %HR by ranges/ linear	Mean ranges/ linear	%H experimental value	Radius %H	"*L*/*S*" function by ranges/ linear	Mean "*L*/*S*" function by *r* %HR
			4.81				6.83	
Vivapur 101 Batch 6610152949	Microcrystalline cellulose	4.695	3.79	4.55	6.74	6.74	5.26	5.64
			5.31				6.02	
Vivapur 102 Batch 5610264136	Microcrystalline cellulose	4.540	3.9	4.68	4.8	7.59	5.75	6.14
			5.46				6.53	
Vivapur 12 Batch 6601260202	Microcrystalline cellulose	4.560	3.89	4.665	7.62	6.19	5.04	5.43
			5.44				5.82	

5. Results and discussion

5.1. Study of the %HR parameter of 22 excipients

The values obtained in the lubricity/stability (L/S) function resulting from the mean of the values of the radii of the %H and %HR parameters (the latter calculated by ranges [nonlinear]) are very similar to the mean of the values for both parameters obtained by means of the linear calculation, as shown in Table 4.

The values of the radius of %HR obtained by means of the linear calculation are only different from the radii obtained by means of the calculation by ranges in the (a) band, i.e. practically with experimental values of %HR of 1 or less (Table 4). Of the 22 excipients studied, only 1 presented a %HR value of less than 1. This excipient was rejected, and the *t* parametric statistical test was carried out on the radius values by ranges and the linear radius values (after performing the F Snededor–Fisher test, the Curtosis test and the Pearson rank correlation test to verify that this test could be applied to these values); a *t* value of 2.00 was obtained, indicating that there are no statistically significant differences between the two groups of radius values ($p > 0.05$). As a result, we can conclude that, provided that the %HR value is greater than 1, the results of the radius will be equivalent when calculated by ranges and when calculated linearly.

Of the 22 excipients studied, it was observed (Table 4) that only one of them presented an experimental %HR value of 1 or less; hence, the incidence in this band is low. When the experimental value of %HR is 1 or less, the experimental value of %H will theoretically be low, as these values are physically correlated: when the radius of %HR is small, the radius of %H is large, its L/S function, which is the mean of both radii, will be compensated and always give values of 5 or higher. As a result, the linear method can also be used to calculate this value, as the effect on the final result will be minimized by the compensation between the parameters (it will not be exactly the same as the result calculated using the ranges method, but, at a practical level, this will not represent a significant variation in the final conclusion). The following observations can be established from the study carried out:

(1) When the L/S function is calculated (the mean of the radii of %HR and %H), the results are very similar for both types of calculation (ranges and linear), i.e. it complies with Eq. (2).

$$\frac{(r\%\mathrm{HR})\mathrm{linear} + (r\%\mathrm{H})}{2} \cong \frac{(R\%\mathrm{HR})\mathrm{ranges} + (r\%\mathrm{H})}{2} \qquad (2)$$

(2) The values of the %HR radius obtained by both types of calculation (ranges and linear) are only different when the experimental value of %HR $\leqslant 1$, i.e. Eq. (2) only fails to be complied with in this case.
(3) The experimental values of %HR obtained in this study are greater than 1 in 95.5% of cases.

Taking into account the experimental results obtained for the 22 excipients studied, we carried out the theoretical calculations using the ranges and linear systems, when the experimental value of the %HR parameter $\leqslant 1$:

(a) with experimental values for %H between 0% and 1%.
(b) with experimental values for %H between 0% and 10%.

Table 5
Theoretical calculations for the %HR parameter with values $\leqslant 1$. Values for %H between 0% and 1%.

%HR value	%H value	%HR radius by ranges	%HR radius linear	%H radius	"L/S" function ranges/linear	*IPP ranges/linear
0.00	0.00	0.00	10.0	10.0	5.00	5.00
					10.00	6.00
0.20	1.00	1.00	9.90	9.50	5.25	5.05
					9.70	5.94
0.40	1.00	2.00	9.80	9.50	5.75	5.15
					9.65	5.93
0.60	1.00	3.00	9.70	9.50	6.25	5.25
					9.60	5.92
0.80	1.00	4.00	9.60	9.50	6.75	5.35
					9.55	5.91
1.00	1.00	5.00	9.50	9.50	7.25	5.45
					9.50	5.90

* To perform these calculations, the other functions (4) were assigned a value of 5.00.

Table 6
Theoretical calculations for the %HR parameter with values ⩽1. Values for %H between 0% and 10%.

%HR value	%H value	%HR radius by ranges	%HR radius linear	%H radius	"L/S" function ranges/linear	*IPP ranges/linear
0.00	0.00	0.00	10.00	10.00	5.00 10.00	5.00 6.00
0.20	1.00	1.00	9.90	9.50	5.25 9.70	5.05 5.94
0.20	2.00	1.00	9.90	9.00	5.00 9.45	5.00 5.89
0.40	3.00	2.00	9.80	8.50	5.25 9.15	5.05 5.83
0.40	4.00	2.00	9.80	8.00	5.00 8.90	5.00 5.78
0.60	5.00	3.00	9.70	7.50	5.25 8.60	5.05 5.72
0.60	6.00	3.00	9.70	7.00	5.00 8.35	5.00 5.67
0.80	7.00	4.00	9.60	6.50	5.25 8.05	5.05 5.61
0.80	8.00	4.00	9.60	6.00	5.00 7.80	5.00 5.56
1.00	9.00	5.00	9.50	5.50	5.25 7.50	5.05 5.50
1.00	10.00	5.00	9.50	5.00	5.00 7.25	5.00 5.45

* To perform these calculations, the other functions (4) were assigned a value of 5.00.

Table 7
APIs of Bioibérica, S.A. Comparison of the calculation of the radius of %HR and of the L/S function by means of the ranges and linear methods.

API	%HR	%H	%HR radius ranges	%HR radius linear	%H radius	Function ranges	Function linear
F0130 Glucosamine CIH 8/0004	0.33	0.00	1.65	9.67	10.00	5.83	9.84
PJ-547 Nucleotides	14.83	3.16	0.00	0.00	8.42	4.21	4.21
F0491 Chondroitin sulfate 100EP 6/0028	8.65	20.73	0.96	1.35	0.00	0.48	0.68
F0168 Glucosamine sodium sulfate 6/0013	0.46	0.28	2.28	9.55	9.86	6.07	9.70
F0192 Glucosamina potassium sulfate 7/0005	0.27	0.20	1.33	9.74	9.90	5.61	9.82
F0324 6/0010	8.21	20.07	1.28	1.79	0.00	0.64	0.90
FT-CS-35 06/90	7.80	17.98	1.57	2.20	1.01	1.29	1.61
FT-CS-35 06/95	7.98	19.80	1.44	2.02	0.10	0.77	1.06
F0349 HYAL-JOINT 5/0026	9.85	16.11	0.11	0.15	1.95	1.03	1.05
F0380 Chondroitin sodium sulfate JP 6/0012	4.43	27.05	3.98	5.57	0.00	1.99	2.79

As shown in Tables 5 and 6, it was observed that, in both systems, the parametric profile index (IPP) gives very similar values, i.e.:

$$\mathrm{IPP}_{r(\mathrm{range})} = \mathrm{IPP}_{l(\mathrm{linear})}$$

5.2. Study of the %HR parameter of 10 APIs

The values obtained in the lubricity/stability (L/S) function resulting from the mean of the values of the radii of the %HR parameter calculated by ranges (nonlinear) are very similar to the mean of the values for both parameters obtained by means of the linear calculation, as shown in Table 7.

Table 7 shows that the mean function obtained from the radii of %HR and %H present similar results using the two systems (ranges and linear).

Hence,

$$\frac{(r\%\mathrm{HR})\mathrm{linear} + (r\%\mathrm{H})}{2} \simeq \frac{(R\%\mathrm{HR})\mathrm{ranges} + (r\%\mathrm{H})}{2}$$

In the same table, it can also be seen that there is an exception to this rule when the experimental value obtained for %HR is less than 1. In this case, as shown in Tables 8 and 9, it will not be necessary to correct the L/S function, as it will always have a value of >5 when the values of the %HR and %H radii balance out, both when the calculation is by ranges and when it is linear. The parametric profile index (IPP = mean of the radii of all the parameters in the SeDeM system, shown in Table 1) will give very similar values when calculated by ranges and when calculated using the linear system (Table 6).

5.3. Comparative calculation of the excipient required for the compression of an API according to the linear method versus the ranges method

We studied the effect on the calculation of the excipient required for the correct compression of the API glucosamine SALT F03657, published in a previous study [3], by comparing the results obtained with the calculation of the radius of the %HR parameter using the linear method compared with the calculation by ranges for the SeDeM Diagram method [1].

To this end, we used the following working methodology:

- Table 10 shows the calculation, using the ranges method, of the necessary percentage of several excipients to correct the deficient compressibility function of API F0357, with a value of

Table 8
APIs and excipients with %HR < 1%. Calculation of the radius of %HR by means of the ranges and linear methods. Comparison of the values of the functions and parametric indexes according to the value of the %HR radius.

Material	%HR	Calculation	Function					Index		
			D	C	F/PF	L/S	L/D	IP	IPP	IGC
F0130 Glucosamine HCI 8/0004	0.33	Ranges Linear	7.98	1.60	2.49	5.83 9.84	5.27	0.42 0.50	4.20 4.87	4.00 4.64
F0168 Glucosamine Na_2SO_4 6/0013	0.46	Ranges Linear	8.78	4.59	1.85	6.07 9.86	4.65	0.42 0.5	4.86 5.47	4.63 5.20
F0192 Glucosamine K_2SO_4 7/0005	0.27	Ranges Linear	9.03	3.95	1.76	5.61 9.82	4.8	0.42 0.5	4.67 5.37	4.44 5.11
Pearlitol 200 SD Batch E165P	0.34	Ranges Linear	5.11	5.12	5.75	5.77 9.75	7.40	0.58 0.67	5.76 6.43	5.49 6.12
Pharmaburst C1 Batch 04K111	1.14	Ranges Linear	5.06	5.89	6.53	6.21 7.79	4.93	0.67 0.67	5.80 6.07	5.52 5.78

Table 9
APIs and excipients with %HR < 1%. Values of the parametric index (IP) according to the calculation of the radius %HR by means of the ranges or linear methods.

Material	Calculation	%HR	%H	*r* %HR	*r* %H	Function	IPP
F0130 Glucosamine HCI 8/0004	Ranges Linear	0.33	0.00	1.64 9.67	10.00	5.83 9.84	0.42 0.50
F0168 Glucosamine Na_2SO_4 6/0013	Ranges Linear	0.46	0.28	2.28 9.55	9.86	6.07 9.70	0.42 0.50
F0192 Glucosamine K_2SO_4 7/0005	Ranges Linear	0.27	0.20	1.33 9.74	9.90	5.61 9.82	0.42 0.50
Pearlitol 200 SD Batch E165P	Ranges Linear	0.34	0.32	1.70 9.66	9.84	5.77 9.75	0.58 0.67

Table 10
Amount of excipient required to ensure that the mixture with the API will give a compressibility mean incidence of 5.

Excipient	Avicel® PH 101	Kleptose®	Kollidon® VA 64	Plasdone® S630	Prosolv® HD90	Isomalt® 721
No.	1	2	3	4	5	6
RE	7.01	7.30	6.93	8.90	5.62	6.11
R P	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 11
Calculation of all mean incidence values resulting from mixing the API with each of the excipients at the concentration levels calculated as per Table 10.

Incidence factor	API	Avicel PH 101	API + Avicel PH 101	Kleptose	API + Kleptose	Kollidon VA 64	API + Kollidon VA 64	Plasdone S630	API + Plasdone S630	Prosolv HD90	API + Prosolv HD90	Isomalt 721	API + Isomalt 721
% Excipient			**44.32**		**41.03**		**45.33**		**29.09**		**72.07**		**59.04**
Dimension	8.88	4.05	6.74	7.02	8.12	2.98	6.21	3.11	7.20	5.41	6.38	5	6.59
Compressibility	3.40	7.01	5.00	7.3	5.00	6.93	5.00	8.9	5.00	5.62	5.00	6.11	5.00
Flowability/ powder flow	4.15	3.01	3.64	4.98	4.49	5.59	4.80	3.04	3.83	6.22	5.64	6.8	5.71
Lubricity/ stability	5.34	6.01	8.33	4.06	8.26	3.02	7.10	3.48	4.80	6.15	8.70	6.95	8.84
Lubricity/ dosage	4.40	6.69	5.41	2.75	3.72	6.95	5.56	4.65	4.47	8.12	7.08	5.50	5.05
Overall mean incidence	5.23	5.35	5.83	5.22	5.92	5.09	5.73	4.64	5.06	6.30	6.56	6.07	6.24

3.4. Table 11 shows the calculated values of the functions of the mixtures of APIs and the different excipients in the percentages shown in Table 10.

- We used the linear method to calculate the value of the radius of the %HR parameter of the API and of the excipients studied. Using these values, we calculated the values of the lubricity/stability function of the API and of the excipients. All these values are shown in Table 12.
- In Table 13, the values of the lubricity/stability function of the API and of the excipients in Table 11 have been replaced with those obtained in Table 12, so that the table shows the values of all the functions of the APIs, excipients and mixtures, calculated using the linear method.

Table 12 shows that the API presents differences in the value of the radii of the %HR parameter between the calculation using the

Table 12
Value of the radius of the %hr parameter and lubricity/stability function of the API and of the excipients studied according to the linear method.

Product	%HR			%H		F "L/S" ranges	F "L/S" linear	Tolerance range (±1)	Variance
	Value	*r* ranges	*r* linear	Value	*r*				
F0357	0.135	0.68	9.87	0.007	10	5.34	9.93	6.64–8.64	10.53405
Avicel PH 101 Batch 64016	4.62	3.84	5.38	3.36	8.17	6.01	6.78	5.40–7.40	0.29645
Kleptose Batch 774639	12.07	0	0	8.12	8.12	4.06	4.06	3.06–5.06	0
Kollidon VA 64 Batch 28–2921	5.54	3.19	4.46	14.31	2.85	3.02	3.65	2.34–4.34	0.19845
Plasdone S630 Batch 6272473	5.25	3.46	6.54	13.66	3.51	3.48	5.02	3.25–5.25	1.1858
Prosolv HD 90 Batch K950044	5.19	3.44	4.81	2.29	8.86	6.15	6.83	5.49–7.49	0.2312
Isomalt 721 Batch RE539	4.39	4.01	5.61	9.89	9.89	6.95	7.75	6.35–8.35	0.32

Table 13
Values of all the functions of the API, excipients and mixtures calculated using the linear method.

Incidence	Problem	Avicel PH101	Mixture 1	Kleptose	Mixture 2	KollVA 60	Mixture 3	Plasd S630	Mixture 4	Prosolv HD90	Mixture 5	Isomalt 721	Mixture 6
% Excipient			**44.32**		**41.03**		**45.33**		**29.09**		**72.07**		**59.04**
Dimensions	8.88	4.05	6.74	7.02	8.12	2.98	6.21	3.11	7.20	5.41	6.38	5	6.59
Compressibility	3.40	7.01	5.00	7.3	5.00	6.93	5.00	8.9	5.00	5.62	5.00	6.11	5.00
Flowability/power flow	4.15	3.01	3.64	4.98	4.49	5.59	4.80	3.04	3.83	6.22	5.64	6.8	5.71
Lubricity/stability	9.93	6.78	8.53	4.06	7.52	3.65	7.08	4.86	8.46	6.83	7.70	7.75	8.64
Lubricity/Dosage	4.40	6.69	5.41	2.75	3.72	6.95	5.56	4.65	4.47	8.12	7.08	5.5	5.05
Mean	6.15	5.51	5.87	5.22	5.77	5.22	5.73	4.91	5.79	6.44	6.36	6.23	6.20

ranges method and the calculation using the linear method and, therefore, also presents differences in the values of the lubricity/stability function calculated using the two different methods. The differences between the values are significant, and this is shown by the values of the variance between both results and by the fact that they are outside the tolerance limits with respect to the mean of both values. This substance shows an experimental value of %HR of less than 1 and will, theoretically, have a low %H value, as these parameters are physically correlated. As a result, when the radius *r* of %HR is low, the radius of %H is high and its lubricity/stability (L/S) function, the mean of both radii, is compensated, giving values of 5 or more. As a result, the linear method can also be used to calculate this value, as the effect on the final result will be minimized by the compensation between the parameters (it will not be exactly the same as the result calculated using the ranges method, but, at a practical level, this will not represent a significant variation in the final conclusion).

Table 12 shows that, although the values of the function obtained by the two methods are different, in both cases, they are greater than 5, thereby making this parameter correct for the SeDeM system.

In the excipients studied, the values of %HR are all greater than 1.5% and, as shown in Table 12, the results of the calculation of the radii and of the function using the ranges or linear method are very similar and within the tolerance limits, with respect to the mean of both values.

The deficiency of the API in obtaining a good profile for direct compression must involve correcting the compressibility function, as its value is 3.4 – the lowest of all its functions.

Table 11 shows the results of the calculation, using the ranges method, for the necessary percentage of several excipients to correct the deficient compressibility function of API F0357. In the calculation carried out using the linear method (Table 13), it can be seen that the corrective quantities of the excipient to be used do not vary in any case, so that the choice of Plasdone S630 does not differ as much when the ranges method is used as when the linear method is used, as it is the excipient that is used in the smallest proportion. In terms of the values of the L/S function, those in Table 13 are higher (linear model), so that the neither the choice of excipient nor its percentage will vary. As a result, it is confirmed that the variation proposed will not alter the use and the results of the SeDeM Diagram proposed in previous studies, but it does simplify its practical application.

The change in the method for calculating the %HR radius and the L/S function from the ranges method to the linear method does not involve differences in the decision regarding the excipient chosen in the article [2] or in the calculation of the percentage used to correct API F0357. According to the results obtained in this study, the change of the method for calculating the radius of %HR may be linear, as it does not interfere with the decision regarding the choice of the right excipient to correct the profile of the API for direct compression or regarding the proportion of the excipient, and it greatly facilitates the calculation of the radii of the %HR parameter and the L/S function in the mixtures.

6. Conclusions

1. The stability (L/S) function, which is the mean of the parameters % relative humidity (%HR) and hygroscopicity (%H), presents statistically equivalent results regardless of whether the calculation is carried out using the ranges method or the linear method, as there are no statistically significant differences.
2. The values of the radius (%HR) obtained by means of the linear calculation and the calculation by ranges are only different when the experimental values of relative humidity (%HR) are 1 or less. This situation, however, is exceptional.
3. It can be seen that when the experimental value of %HR is 1 or less, the experimental value of %H will theoretically be low, as these values are physically correlated. As a result, when the radius *r* of %HR is low, the radius of %H is high and the mean of the L/S function is compensated.
4. Therefore, when determining the %HR radius of an API, when the experimental value is less than 1, it will not be necessary to correct the L/S function to achieve good compression, as it will always have a value of 5 or greater, regardless of whether the linear or ranges calculation method is used. Furthermore, when both calculation methods are used to determine the %HR radius of the APIs, the results of the parametric profile indexes (IPP) are similar.

5. The observations carried out show that the results obtained by applying either of the two calculation systems present no significant differences and do not alter the compression profile of the product studied (APIs or excipients for direct compression).
6. We propose modifying the SeDeM Diagram Expert System for the parameter corresponding to the Hausner index by establishing limit values that should be between 3 and 1 (3 corresponds to a radius of 0 and 1 corresponds to a radius of 10). Exceptional values of less than 1 should be considered as values corresponding to nonflowing or almost nonflowing products that would have a radius of zero. The new equation for resolution is 10-(10V/3).
7. We propose modifying the SeDeM Diagram Expert System for the parameter corresponding to % relative humidity (%HR) by establishing that it should be determined by means of simple linear calculation and taking into account a single range of between 10 and 0 and applying r = 10-V, where V = experimental value.
8. For the parameter corresponding to % relative humidity (%HR) in the SeDeM Diagram Expert System, we propose applying the method of calculation by ranges only for those special cases where compressibility is of critical importance.
9. We propose adopting the linear method for calculating the radius of %HR, as it does not affect the decision regarding the choice of the appropriate excipient to correct the profile for direct compression of an API or regarding the proportion of the API in comparison with the ranges method.

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