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Research paper

Application of the SeDeM Diagram and a new mathematical equation in the design of direct compression tablet formulation

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Abstract

Application of the new SeDeM Method is proposed for the study of the galenic properties of excipients in terms of the applicability of direct-compression technology. Through experimental studies of the parameters of the SeDeM Method and their subsequent mathematical treatment and graphical expression (SeDeM Diagram), six different DC diluents were analysed to determine whether they were suitable for direct compression (DC). Based on the properties of these diluents, a mathematical equation was established to identify the best DC diluent and the optimum amount to be used when defining a suitable formula for direct compression, depending on the SeDeM properties of the active pharmaceutical ingredient (API) to be used. The results obtained confirm that the SeDeM Method is an appropriate system, effective tool for determining a viable formulation for tablets prepared by direct compression, and can thus be used as the basis for the relevant pharmaceutical development.

Keywords: Expert system; SeDeM; Formulation; Bulk Density (Da); Tapped Density (Dc); Inter-particle Porosity (Ie); Angle of Repose (α); Flowability (*t''*); Particle Size (%Pf); Direct compression (DC)

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 or excipients in powder form for direct compression. This information indicates the degree to which substances can be successfully compressed by means of direct-compression technology. The SeDeM Method makes it possible to detect the properties of the powder that need to be adjusted to facilitate 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 for preparing a powder substance and, consequently, for validating the preparation system [2].

This paper examines the applicability of the SeDeM Method to the characterization of the galenic properties of six DC diluents, with an experimental study of the parameters used in the SeDeM Diagram, which are then quantified to create the definitive SeDeM Diagram. The API under study is glucosamine salt F0357, chosen as the model because it is required in high doses in tablets (about 750 mg) and presents poor rheological properties and poor compressibility. Based on the results obtained, a mathematical equation is determined to calculate the approximate amount of excipient required to correct the deficient API parameters and thereby achieve direct compression.

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The theoretical amount obtained as a result of these mathematical calculations is then studied experimentally, and the mixture of excipient and API is used to prepare the relevant SeDeM Diagram and quantify the galenic-characterization parameters. This is used to validate the theoretical model, and the applicability of the SeDeM Method is thus demonstrated in studies of the preformulation and formulation of tablets through direct compression.

2. Product characterization using the SeDeM Method

As established in earlier papers [1,2], the SeDeM Method is based on the experimental study and quantitative determination of the characterization parameters of substances in powder form that provide the necessary information about the appropriateness of the said substances for obtaining tablets by direct-compression technology. Said 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 (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 equations [1,2] and duly validated, reproducible experimental tests, as shown in Table 1.

Eq. (1) named in Table 1 is

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

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 under study, within a series, with respect to the majority fraction.

d_m Mean diameter of the particles in the majority fraction.

Table 1
Parameters and equations used in SeDeM methodology

Incidence factor	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
	Hygroscopicity	%H	%	Experimental
Lubricity/Dosage	Particles < 50 μm	%Pf	%	Experimental
	Homogeneity Index[b]	($I\theta$)	–	Eq. (1)

[a] Hardness (N) of the tablets obtained with the product in question, alone or blended with lubricants if highly abrasive.

[b] Determines Particle Size, in accordance with the percentages of the different particle-size fractions, by applying Eq. (1).

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.

3. Materials and methods

3.1. Materials

The material under study was glucosamine salt F0357 (Bioibérica, S.A., Spain), an API of natural origin used in the treatment of rheumatic and arthritic disorders [3–6] and administered in the form of tablets, capsules and solutions.

The DC excipients used were Microcrystalline cellulose (Avicel® PH 101, FMC Corp, Brusseles, Belgium); β-cyclodextrin (Kleptose®, ROQUETTE, Roquette Frères, Lestrem, France); Copovidone (Kollidon® VA 64, BASF, Ludwigshafen, Germany); Copovidone (Plasdone® S630, ISP, Koln, Germany); Microcrystalline cellulose and SiO_2 (Prosolv® HD90, JRS, Rosenberg, Germany) and Glucopyranosyl-mannitol/sorbitol (Isomalt® 721, GalenIQ, Manheim, Germany).

Other excipients used in the formulations were Talc (Fagron, Barcelona, Spain); Magnesium stearate (Fagron, Barcelona, Spain) and Silica colloidal (Degussa-Hüls, Darmstadt, Germany).

3.2. Methods

3.2.1. Galenic characterization

The procedure for the galenic characterization of these substances requires the parameters of the SeDeM Diagram to be determined [1,2]. Whenever possible, the methods indicated in pharmacopoeias are applied. When these are not available, a system based on the usual practice followed in galenic research is proposed, adapted specifically for the SeDeM Diagram [1,2].

3.2.2. Blends preparation

API and excipient blends obtention on application SeDeM Diagram were prepared following the next steps: weight all the substances up to the calculated quantity, pass them through a 600 μm sieve and mix together in a biconic mixer (Glatt® Labortechnic, Spain) for 20 min.

3.2.3. Tablets preparation

The proposed formulation was compressed in a Bonals® (Cornellà de Ll., Spain) continuous eccentric press, provided with 19 × 10 mm punches.

3.2.4. Tablets characterization

In the characterization of the tablets the methods applied were Uniformity of mass [7], Resistance to crushing of tablets [8], Friability [9] and Disintegration [10].

4. Results and discussions

4.1. SeDeM Diagram results for the API and DC excipients

The parameter values were obtained in accordance with the described methodology, and each of the Diagram radii was calculated by applying the equations in Table 1, the values obtained being converted into radii (r), as shown in Tables 2 and 3.

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

The corresponding parameters and the mean radius values obtained with the samples of the API F0357 are shown in Table 4. The parameters and the mean radius values of the six DC excipients are shown in Tables 5 and 6.

The SeDeM Diagrams showing the results of the mean radii of the three values or replicates for each substance are shown in Figs. 1–7.

Table 2
Conversion of limits for each parameter into radius values (r)

Incidence factor	Parameter	Limit value (V)	Radius (r)	Factor applied to v
Dimensions	Bulk Density	0–1	0–10	10 v
	Tapped Density	0–1	0–10	10 v
Compressibility	Inter-particle Porosity	0–1.2	0–10	10 v/1.2
	Carr Index	0–50	0–10	v/5
	Cohesion Index	0–200	0–10	v/20
Flowability/Powder Flow	Hausner Ratio	3–0	0–10	10 − (10 v/3)
	Angle of Repose	50–0	0–10	10 − (v/5)
	Powder Flow	20–0	0–10	10 − (v/2)
Lubricity/Stability	Loss on Drying[a]	0–1–2–3–10	0–5–10–0	[a]
	Hygroscopicity	20–0	0–10	10 − (v/2)
Lubricity/Dosage	Particles < 50 μm	50–0	0–10	10 − (v/5)
	Homogeneity Index	0–2 × 10^{-2}	0–10	500 v

[a] Calculate r for the Loss on Drying parameter as indicated in Table 3, in accordance with the value obtained and as described in the previous paper on the subject [1].

Table 3
Calculation of r based on the Loss on Drying value

	Description	Range (a)	Range (b)	Range (c)
Range of values	Range value interval	0–2	3–10	2–3
	Radius (r) range to be applied	0–10	5–0	10–0
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	$r = (R_{max}\ V)/(V_{max})$	$r = (R_{max}(V_{max} - V))/(V_{max} - V_{min})$	

Table 4
Parameters, mean incidence values and parametric index for API F0357

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	–	1.471	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	%	0.135	0.68	5.34
	Hygroscopicity	%H	%	0.007	10.00	
Lubricity/Dosage	Particles < 50 μm	%Pf	%	12.000	7.60	4.40
	Homogeneity Index	($I\theta$)		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 5
Value parameters, mean incidence values and parametric index for DC excipients

Excipient	Parameters (value)											
	Da	Dc	Ie	IC	Icd	IH	(α)	t''	%HR	%H	%Pf	($I\theta$)
Avicel® PH 101	0.347	0.463	0.722	25.054	263.500	1.334	32.690	20.000	4.620	3.660	33.100	0.0316
Kleptose®	0.558	0.846	0.610	34.043	318.000	1.516	32.460	7.000	12.070	3.770	32.000	0.0038
Kollidon® VA 64	0.253	0.343	1.037	26.239	138.200	1.356	19.860	9.500	5.540	14.310	8.000	0.0110
Plasdone® S630	0.248	0.373	1.351	33.512	300.000	1.504	29.340	20.000	5.150	13.660	32.000	0.0114
Prosolv® HD90	0.486	0.596	0.380	18.455	409.680	1.226	20.075	6.500	5.190	2.290	18.800	0.0443
Isomalt® 721	0.440	0.560	0.487	21.429	362.400	1.273	18.780	6.300	4.390	0.230	5.000	0.0040

4.2. Selection of the most suitable DC excipient for the compression of API F0357

A study of the SeDeM Diagram for API F0357 (Fig. 1, Table 4) indicates that it is a substance with poor compressibility properties (mean incidence radius = 3.40), limited rheological properties (mean incidence radius = 4.15) and low Lubricity/Dosage indices (mean incidence radius = 4.40). As a result, in order to be able to formulate a suitable blend for direct compression with API F0357, an excipient must be used which, when used in the smallest possible quantity, improves the poor SeDeM indices and parameters, and particularly the compressibility parameter.

A new equation is proposed (Eq. (2)) for the selection of the excipient and the concentration in which it is required in order to correct the poor characteristics observed, particularly the compressibility parameter. The equation was originally specifically designed for this purpose and is intended for use in calculating the amount of excipient required to compress the API, based on the SeDeM radius regarded as the minimum necessary for each incidence parameter in order to ensure successful compression.

$$\mathrm{CP} = 100 - \left(\frac{\mathrm{RE} - R}{\mathrm{RE} - \mathrm{RP}} \times 100\right), \tag{2}$$

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.

Once the unknown values in Eq. (2) have been replaced with the calculated values required for each substance in order to obtain $R = 5$ (5 is the minimum value that is regarded as necessary in order to achieve good compression), the results shown in Table 7 are obtained.

As may be concluded from Table 7, of the preselected group of excipients, Plasdone® S630 is the most suitable for correcting the deficient incidence (compressibility) of API F0357, given that the incidence value $R = 5$ was obtained with the lowest level of concentration (29.09%).

Having selected this excipient (Plasdone® S630), its influence on the other incidence factors of API F0357 in the theoretical blend (dimensions, flowability, stability, dosage) can be confirmed, along with its now corrected compressibility, and it can be compared with blends using the other excipients

Table 6
Radius parameters, mean incidence values and parametric index for DC excipients

Excipient	Parameters (r)										Mean incidence				Index		
	Da	Dc	Ie	IC	Icd	IH	(α)	t''	%HR	%H	%Pf	(Iθ)	Dimension	Compressibility	Flowability/ Powder Flow	Lubricity/ Sability	Lubricity/ Dsage	IP	PP	IGC
Avicel® PH 101	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	6.01	6.69	0.0	5.29	5.04
Kleptose®	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	4.06	2.75	0.58	5.38	5.12
Kollidon® VA 64	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	3.02	6.95	0.67	5.29	5.03
Plasdone® S630	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	3.32	4.65	0.33	4.83	4.60
Prosolv® HD90	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	6.15	8.12	0.67	6.24	5.94
Isomalt® 721	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	6.95	5.50	0.58	6.01	5.72

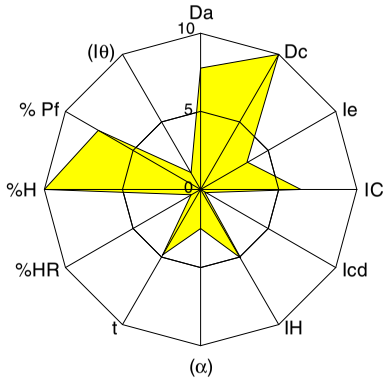

Fig. 1. SeDeM Diagram for API F0357.

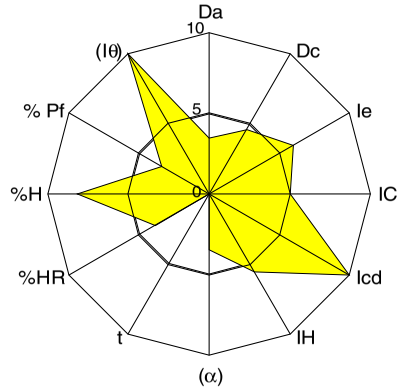

Fig. 2. SeDeM Diagram for Avicel® PH 101.

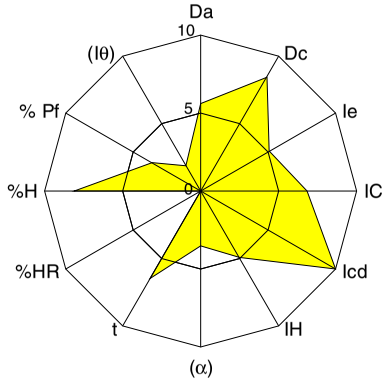

Fig. 3. SeDeM Diagram for Kleptose®.

from the group in the concentration levels stipulated in Table 7. These results are shown in Table 8, which also shows the mean value of all the medians in each theoretical blend. They are calculated using Eq. (2), in which the value CP is replaced with the concentration level obtained for each excipient, thus revealing value *R*.

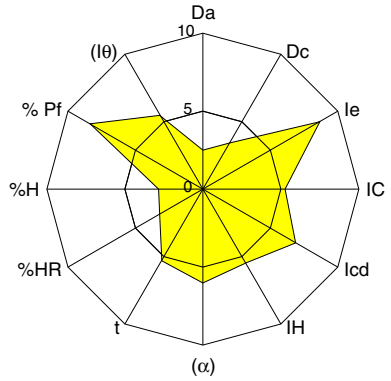

Fig. 4. SeDeM Diagram for Kollidon® VA64.

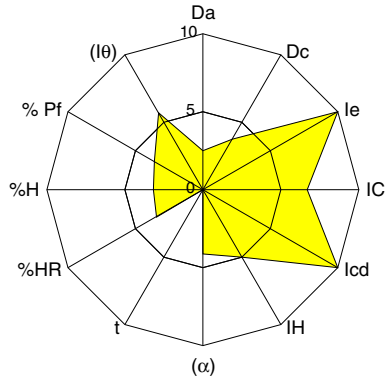

Fig. 5. SeDeM Diagram for Plasdone® S630.

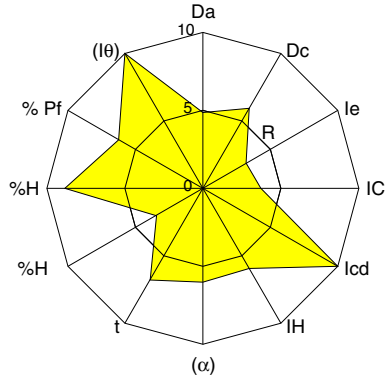

Fig. 6. SeDeM Diagram for Prosolv® HD90.

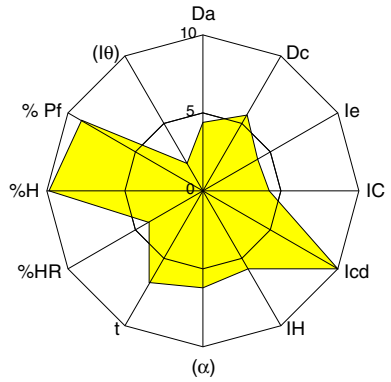

Fig. 7. SeDeM Diagram for Isomalt® 721.

It should be stressed that the %HR parameter is calculated differently depending on the scale used, given that the percentage ratio obtained by calculating the humidity of the substance being analysed does not maintain a linear relationship with the correct performance of the powder [1].

Thus, when a Lubricity/Stability mean incidence involves a blend in which the %HR parameter values correspond to different scales for radius calculation as per the SeDeM Diagram (as indicated in Table 3).

(1) Calculate the %HR of the blend, bearing in mind the proportions and %HR of each of its components.
(2) Calculate the value of the %HR parameter radius on the relevant scale, based on the %HR value for the blend, as calculated in Point 1.
(3) Calculate the %H of the blend, bearing in mind the proportions and %H of each of its components.
(4) Calculate the value of the %H parameter radius, based on the %H value for the blend, as calculated in Point 3.
(5) Calculate the mean value of the radii obtained in Points 2 and 4, thus obtaining the theoretical value that corresponds to the Lubricity/Stability mean incidence.

By way of example, the following shows the equation applied to a blend of API F0357 (70.91%) and Plasdone® S630 (29.09%) (Blend 4, Table 7).

In this case, the humidity value of API F0357 which is shown in Table 4 is 0.135 (scale 0–2 in the parameter radius calculation when calculated in accordance with Table 3) [1], while the value for Plasdone® S630 (which is shown in Table 5) is 5.15 (scale 3–10 when calculated in accordance with Table 3).

(1) Calculation of the % relative humidity of the blend (the %HR values are shown in Tables 4 and 5):
((%API × %HR API)/100)) + ((%Plasdone® × %HR Plasdone®)/100))
i.e. ((70.91 × 0.135)/100 + (29.09 × 5.15)/100) = 1.593.
(2) On the 0 to 2 scale, a SeDeM radius of 7.97 corresponds to a %HR of 1.594.
(3) Calculation of the %H of the blend:
((%API × %H API)/100)) + ((%Plasdone® × %H Plasdone®)/100))
i.e. ((70.91 × 0.007/100 + (29.09 × 13.66)/100) = 3.979.
(4) According to Table 2, a SeDeM radius of 8.01 corresponds to a %H of 3.979.
(5) The average value of the radii for the %HR and %H parameters for the blend (7.97 and 8.01, respectively) will be 7.99.

The theoretical value that corresponds to the resulting Lubricity/Stability mean incidence is 7.99, the value that will be shown in Tables 8 and 11.

Table 7
Amount of excipient required in order to ensure that 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 (CP)	44.32	41.03	45.33	29.09	72.07	59.04

Table 8 shows that, of the averages obtained from the mean values for each of the incidence values studied, the one that displays the highest value is not Plasdone® S630, value 5.70 (Blend 4), but Prosolv® HD90 (Blend 5), which gives a value of 6.56. However, bearing in mind that API F0357 must be used in very high doses of about 750 mg, Plasdone® S630 is preferred at a concentration level of 29.09%, as this would make it possible to obtain tablets weighing between 1 and 1.5 g, whereas with Prosolv® HD90 tablets of around 3 g would have to be prepared.

It can also be seen from Table 8 that the influence of 29.09% Plasdone® S630 on the other incidence factors shows values that remain within the acceptable limits set (5 ± 1), with the exception of flowability, which can be easily corrected using a suitable lubricant that is effective at concentration levels of around 3%.

As a result, Plasdone® S630 is chosen as the most suitable excipient for use in the compression of API F0357.

The SeDeM Diagrams in Figs. 8–13 show the radius values for each excipient superimposed on those of API F0357 in order to illustrate the influence of the parameters of each excipient on those of the API and, therefore, their influence on the properties of the product. They confirm that Plasdone® S630 is a suitable excipient for use in the compression of the API examined, particularly because it corrects the most deficient parameters.

4.3. API–Plasdone® S630 formulation test and SeDeM characterization

Once the most suitable excipient has been selected using the SeDeM Method, its experimental values are established using the same method in order to validate the proposed theoretical model. A blend is therefore prepared using API F0357 (70.91%) and Plasdone® S630 (29.09%), and the SeDeM Diagram is applied to obtain the parameter values (Table 9) that will be used to construct Fig. 14.

It is observed that the mean incidence values from the radii obtained in the test using the API and Plasdone® S630 blend are very similar to the mean incidence values obtained from the theoretical calculation in respect of this blend, bearing in mind the acceptable value interval (± 1) as per the limits established [2].

Bearing in mind that lubricants and freeflow agents are required in any compression process, a blend of API F0357 and Plasdone® S630 is prepared, from which 3.50% of the excipient is removed and replaced with a lubricant mixture of talc (2.36%), colloidal silica 200 (0.14%) and magnesium stearate (1.0%). The values and SeDeM radii obtained from this blend are shown in Table 10 and Fig. 15.

4.4. Experimental confirmation of the theoretical formula

Once the test has been completed, the theoretical values (Table 8) are compared with the values obtained from the experiment using the F0357 (70.91%)/Plasdone® S630 (29.09%) blend as per Table 11 and the F0357 (70.91%)/Plasdone® S630 (25.59%)/Lubricants (3.5%) blend as per Table 12.

Both tables show the values obtained from the statistical treatment of the test values obtained with the F0357 + Plasdone® S630 (29.09%), in Table 9, blend and the F0357 + Plasdone® S630 (25.59%) + lubricant blend, compared with the theoretical value (calculated blend value) calculated in both cases. The statistical treatment applied was based on Student's *t*-test parametric analysis and the non-parametric analysis of the sign test, and it was found in all cases that there were no statistically significant differences between the test values and the theoretical value calculated ($p > 0.05$). As a result, it was shown that the proposed theoretical model provides correct, reliable results that are in line with the test results, and the model can therefore be regarded as valid. These results are in keeping with the specifications of ± 1.0 established for the parameters of the SeDeM Diagram [2].

The individual parameters of the theoretical results are not given, nor is a diagram drawn, since the percentages of the corrective excipients were calculated on the basis of the mean incidence values of both the API under study and the excipient.

4.5. Manufacture of tablets using the proposed formula

In order to confirm that the proposed theoretical formula gives the right results in the compression process,

Table 8
Calculation of all mean incidence values resulting from mixing the API with each of the excipients at the concentration levels calculated as per Table 7

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[a]	5.34	6.01	8.33	4.06	8.26	3.02	7.10	3.32	7.99	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	4.60	5.70	6.30	6.56	6.07	6.24

[a] The Lubricity/Stability mean incidence is calculated from the radius obtained using the theoretical values of the humidity and hygroscopicity parameters of the blends.

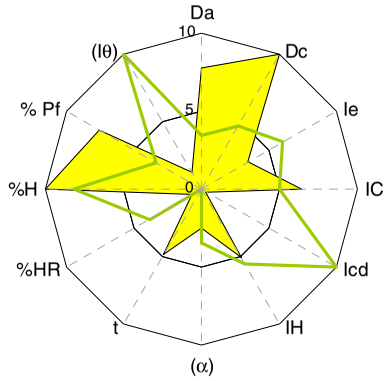

Fig. 8. Superimposition of the SeDeM Diagram for Avicel® PH 101 on the SeDeM Diagram for API F0357.

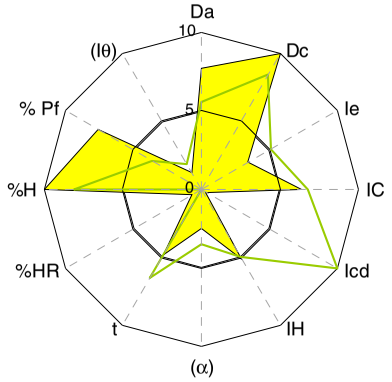

Fig. 9. Superimposition of the SeDeM Diagram for Kleptose® on the SeDeM Diagram for API F0357.

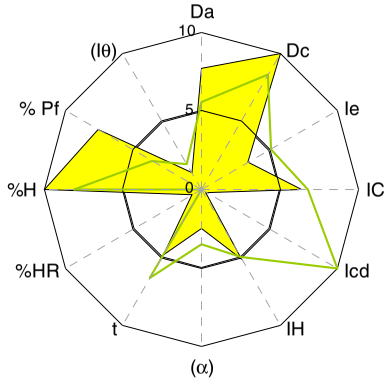

Fig. 10. Superimposition of the SeDeM Diagram for Kollidon® VA64 on the SeDeM Diagram for API F0357.

500 g of a blend of F0357 (70.91%), Plasdone® S630 (25.59%) and a combination of lubricants (3.50%) was prepared for compression in a Bonals continuous eccentric press with 19 × 10 mm punches. Examination of the tablets obtained gave the following results:

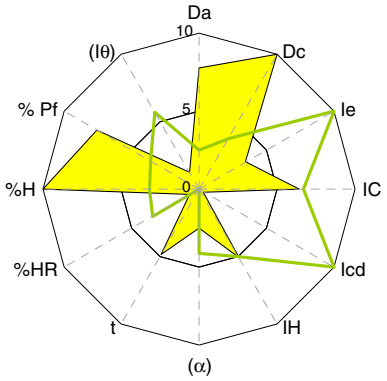

Fig. 11. Superimposition of the SeDeM Diagram for Plasdone® S630 on the SeDeM Diagram for API F0357.

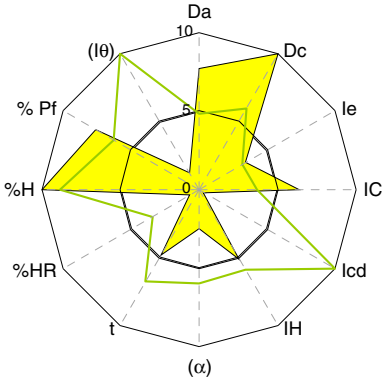

Fig. 12. Superimposition of the SeDeM Diagram for Prosolv® HD90 on the SeDeM Diagram for API F0357.

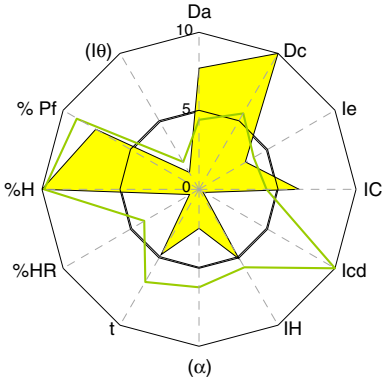

Fig. 13. Superimposition of the SeDeM Diagram for Isomalt® 721 on the SeDeM Diagram for API F0357.

Uniformity of mass:
Average = 1021.32 mg
$S_{n-1} = 14.14$
CV% = 1.38%
Resistance to crushing of tablets:

Table 9
Parameters, mean incidence values and indices of a blend containing API F0357 (70.91%) and Plasdone® S630 (29.09%)

Incidence factor	Parameter	Symbol	Unit	Value (v)	(r)	Mean incidence
Dimension	Bulk Density	Da	g/ml	0.526	5.26	6.36
	Tapped Density	Dc	g/ml	0.746	7.46	
Compressibility	Inter-particle Porosity	Ie	–	0.561	4.67	6.32
	Carr Index	IC	%	29.491	5.90	
	Cohesion Index	Icd	N	167.800	8.39	
Flowability/ Powder Flow	Hausner Ratio	IH	–	1.418	5.27	5.07
	Angle of Repose	(α)	°	31.990	3.60	
	Powder Flow	t	s	7.333	6.33	
Lubricity/ Stability	Loss on Drying	%HR	%	1.540	7.70	8.01
	Hygroscopicity	%H	%	3.375	8.31	
Lubricity/ Dosage	Particles < 50 μm	%Pf	%	15.000	7.00	4.23
	Homogeneity Index	($I\theta$)		0.0029	1.45	
Parameter index					0.75	
Parametric profile index (mean r of all parameters)					5.95	
Good compression index (IGC)					5.66	

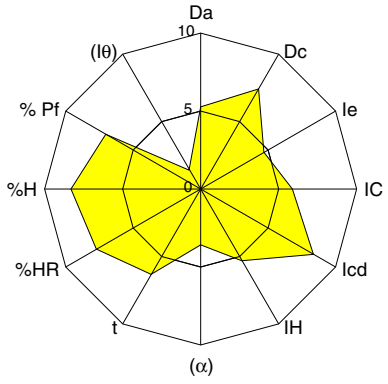

Fig. 14. SeDeM Diagram for a blend containing API F0357 (70.91%) and Plasdone® S630 (29.09%).

Table 10
Parameters, mean incidence values and indices for a blend containing API F0357 (70.91%), Plasdone® S630 (25.59%) and a combination of lubricant excipients (3.50%)

Incidence factor	Parameter	Symbol	Unit	Value (v)	(r)	Mean incidence
Dimension	Bulk Density	Da	g/ml	0.657	6.57	7.47
	Tapped Density	Dc	g/ml	0.837	8.37	
Compressibility	Inter-particle Porosity	Ie	–	0.327	2.73	5.68
	Carr Index	IC	%	21.505	4.30	
	Cohesion Index	Icd	N	214.600	10.00	
Flowability/ Powder Flow	Hausner Ratio	IH	–	1.274	5.75	6.57
	Angle of Repose	(α)	°	26.900	4.62	
	Powder Flow	t	s	1.333	9.33	
Lubricity/ Stability	Loss on Drying	%HR	%	2.660	6.70	7.75
	Hygroscopicity	%H	%	2.400	8.80	
Lubricity/ Dosage	Particles < 50 μm	%Pf	%	22.000	5.60	3.65
	Homogeneity Index	($I\theta$)		0.0034	1.70	
Parameter index					0.67	
Parametric profile index (mean r of all parameters)					6.21	
Good compression index (IGC)					5.91	

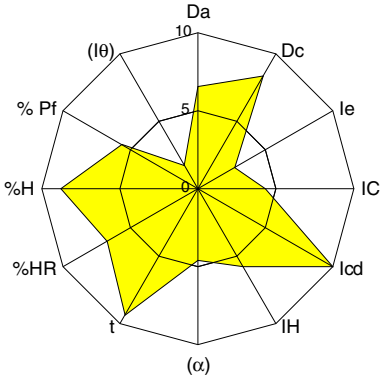

Fig. 15. SeDeM Diagram for a blend containing API F0357 (70.91%), Plasdone® S630 (25.59%) and a combination of lubricant excipients (3.5%).

Average = 188 N
S_{n-1} = 6.27%
CV% = 3.33%
Friability: 0.40%
Disintegration: 9–11 min

The results obtained from an examination of the tablets show that the blend studied produces tablets that are acceptable from a galenic point of view, and that the SeDeM Method can guide and facilitate the design of a basic tablet formulation that can be used to develop a good direct-compression formula. From this point, an assessment should be made regarding the addition of disintegrant and other excipients in order to arrive at the final formula.

5. Conclusions

1. The SeDeM Diagram is a useful tool for the galenic characterization of excipients with respect to their suitability for direct compression.
2. A SeDeM mathematical model is established that provides for identifying the best excipient and calculating the maximum amount of this excipient required for the direct compression of an API, based on the characteristics modelled in the SeDeM Diagram.
3. The SeDeM Diagram expert system provides for determining a preliminary formulation that is suitable for direct compression, from which the relevant galenic development can be made.
4. Glucosamine salt API F0357, which presents poor properties for direct compression, can be submitted to direct compression when a small quantity (29.09%) of the excipient Plasdone® S630 is added.

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Table 11
Comparison of the theoretical and test results of the F0357 + Plasdone® S630 (29.09%) blend

Mean incidence	F0357	Calculated blend value	F0357 + Plasdone®	*t*-Test			Sign test		
				t-Statistic	*P*-Value	Significance	Large sample test statistic	*P*-Value	Significance
Dimension	8.88	7.20	6.36	1.474	0.230	NS	0.000	1.000	NS
Compressibility	3.40	5.00	6.32	0.774	0.480	NS	0.666	0.500	NS
Flowability/Powder Flow	4.15	3.83	5.07	1.877	0.130	NS	0.755	0.440	NS
Lubricity/Stability[a]	5.34	7.99[a]	8.01	0.156	0.890	NS	0.000	0.999	NS
Lubricity/Dosage	4.40	4.47	4.23	0.088	0.940	NS	0.000	1.000	NS

[a] The Lubricity/Stability mean incidence is calculated from the radius obtained using the theoretical values of the humidity and hygroscopicity parameters of the blends, as indicated in the footnote to Table 8.

Table 12
Comparison of the theoretical and test results of the F0357 + Plasdone® S630 (25.59%) + lubricant blend (3.50%)

Mean incidence	F0357	Calculated blend value	F0357 + Plasdone® + lubricant	*t*-Test			Sign test		
				t-Statistic	*P*-Value	Significance	Large sample test statistic	*P*-Value	Significance
Dimension	8.88	7.20	7.47	0.522	0.637	NS	0.000	1.000	NS
Compressibility	3.40	5.00	5.68	0.134	0.890	NS	0.894	0.370	NS
Flowability/Powder Flow	4.15	3.83	6.57	2.502	0.060	NS	1.788	0.070	NS
Lubricity/Stability[a]	5.34	7.99[a]	7.75	0.599	0.600	NS	0.000	0.999	NS
Lubricity/Dosage	4.40	4.47	3.65	0.420	0.740	NS	0.000	1.000	NS

[a] The Lubricity/Stability mean incidence is calculated from the radius obtained using the theoretical values of the humidity and hygroscopicity parameters of the blends, as indicated in the footnote to Table 8.

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