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Comparison between Microcrystalline Celluloses of different grades made by four manufacturers using the SeDeM diagram expert system as a pharmaceutical characterization tool

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ABSTRACT

The characterization of pharmaceutical powders by means of the SeDeM diagram expert system allows developing a database. This database is a useful tool in pre-formulation steps as initial screening for suitable filler excipients. This study compiles the characterization of 21 powdery Microcrystalline Celluloses (MCC) of different grades (101, 102, 301, 302 and 200) made by four different manufacturers (FMC Biopolymer, Ming Thai Co., Blanver, and JRS Pharma). The SeDeM characterization led to describing and to analysing the differences between each MCC studied. From this characterization, five Incidence means (Dimensions, Compressibility, Flowability, Lubricity/Stability and Lubricity/Dosage) and the Index of Good Compression (IGC) are calculated. If the IGC is below 5, the SeDeM diagram indicates that the powdery substance is not suitable for direct compression technology. The results show that each manufacturer has its own differences between grades: whereas JRS and FMC Biopolymer have well defined differences for each grade, there are no differences between grades 101 and 102 for Ming Thai products; and Blanver's grade 102 is less suitable for direct compression than grade 101. Then, each MCC is compared against the others of the same grade. Although they are usually described by the manufacturers similarly, the results indicate that there may be large differences between them. Finally, the different brands are compared from an overall perspective. The IGC averages for FMC Biopolymer and JRS are acceptable values (above 5). However, Blanver and Ming Thai present deficient values (below 5), though they are still close to the acceptance limit. Thus, it is possible to conclude that the products of JRS and FMC Biopolymer meet the manufacturers' description and seem to be more suitable (higher IGCs) for direct compression than those of Blanver and Ming Thai.

1. Introduction

MCCs are commonly used as filler/binder in direct compression formulations [1,2] owing to their high "Compressibility" and good/acceptable "Flowability" [3–6]. In consequence, there are a wide variety of manufacturers who produce them by different manufacturing techniques or from different raw materials [7–10]. Likewise, a large number of different MCCs are also available in order to meet all customers' formulation requirements (different particle size distribution, different bulk density, mixed with other substances, among others). These and other factors such as their crystallinity, raw material, manufacturing technique and country origin could lead to differences during the tableting process [11–18]. Nonetheless, the product description provided by the different manufacturers does not differ greatly from one to another (concerning the same grade). For instance, four different manufacturers (FMC Biopolymer, Ming Thai Chemical, Blanver, and JRS) offer similar descriptions for their products: grade 101 is described by all four manufacturers as having the finest particle size. It has an average particle size near to 50 μm, except for JRS (65 μm). All the manufacturers suggest this grade for wet granulation, and JRS specifies that its products (Vivapur® 101 and Emcocel® 50 M) have a high compactability. However, this grade is also used in formulations for DC. This is the reason for including it in this study. The manufacturers describe grade 102 as

Abbreviations: Da, Bulk Density; Dc, Tapped Density; Ie, Inter-particle Porosity; IC, Carr Index; Icd, Cohesion Index; IH, Hausner Ratio; α, Angle of Repose; t", Powder Flow; %HR, Loss on Drying; %H, Hygroscopicity; %Pf, Particle Size; IΘ, Homogeneity Index; MCC, Microcrystalline Cellulose; API, Active Pharmaceutical Ingredient; DC, Direct Compression.

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having a larger average particle size (near to 100 μm for most grades and 130 for JRS's products) and it is suggested for direct compression. Grades 301 and 302 are described as the same quality as grades 101 and 102, and are therefore recommended for the same procedures, but with a higher bulk density. Grade 200 is described as the largest average particle size (180 μm by most brands, but 220 μm and 250 μm for Emcocel® LP 200 and Vivapur® 200, respectively). Due to its superior flow, the manufacturers describe it as being the excipient of choice to correct the API's flow deficiencies. Moreover, they suggest this grade for DC because it displays good compactability. It should be pointed out that Ming Thai Chemical does not suggest any application for its grades. It merely describes its products' characteristics and specifications.

In this study, SeDeM characterization was done for the grades described above produced by the four manufacturers.[1] The SeDeM Methodology [19] is a pharmaceutical method applicable in tablet formulation studies. It characterizes powders such as excipients or drug substances. This characterization provides information in diagram form about substances' suitability for successful direct compression (DC). The knowledge of a powder's deficiencies facilitates the formulation of a final blend which is able to correct them. As established in earlier studies [19–29], SeDeM characterization obtains the necessary information about a substance's suitability for achieving tablets using direct compression technology. The following parameters are considered:

- 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 (IΘ)

These parameters are determined by means of the SeDeM Diagram method, based on known equations [22], and duly validated reproducible experimental tests, as shown in Table 1.

Once the parameters of the SeDeM Diagram had been established, the acceptable numerical limit values for each of the 12 study parameters were selected. These values are shown in Table 2.

If all radius values are 10, the SeDeM diagram creates a twelve-side regular polygon as a result of attaching the different radii by linear segments. The previous experimental values are converted into radius values and the figure created describes the product characteristics. Each parameter indicates whether the powder is suitable for direct compression. The SeDeM diagram used in this study consists of 12 parameters or, in other words, it is formed by 12 sides. In order to determine numerically whether the product is suitable for direct compression or not, the following indexes are calculated:

$$Parameter\ Index\ (IP) = \frac{No.Pt \geq 5}{No.Pt}$$

No. Pt ≥ 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 ≥ 0.5.

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

Mean r = mean value of the parameters calculated.

[1] Grades 301 and 302 for Blanver and grade 200 for Ming Thai Chemical were not available.

Table 1
Parameters and equations used in SeDeM methodology.

Incidence	Parameter	Symbol	Unit	Equation
Dimension	Bulk Density	Da	g/mL	Da = M/Va
	Tapped Density	Dc	g/mL	Dc = M/Vc
Compressibility	Inter-particle Porosity	Ie	-	Ie = (Dc-Da)/(DcxDa)
	Carr Index	IC	%	IC = (Dc-Da)/Dcx100
	Cohesion Index[a]	Icd	N	Experimental
"Flowability"/Powder flow	Hausner Index ratio	IH	-	IH = Dc/Da
	Angle of Repose	(α)	°	Tgα = 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]	(IΘ)	-	IΘ = Fm/100 + ΔFmn[a]

[a] Hardness (N) of the tablets obtained with the tested product, alone or blended with lubricants if highly abrasive.
[b] Determines particle size in accordance with the percentages of the different particle size fractions.

The acceptability limit would correspond to: IPP ≥5.
Index of Good Compression (IGC) is calculated as follows:

$$Index\ of\ Good\ Compression = IPP \times f$$

Where f is the reliability factor and is calculated as follows:

$$f = \frac{Polygon\ area}{Circle\ area}$$

The acceptability limit would correspond to: IGC ≥ 5.

If the IGC or a high number of parameters are below 5, the SeDeM diagram indicates that the powdery substance is not suitable for direct compression technology and several problems may arise during compression.

The aim of this study is to compare similar products offered by different manufacturers, often described similarly, from a database obtained by means of SeDeM characterization. The comparison allows verifying whether the different products fulfil the manufacturer's description, they are equivalents or not, and how these differences could affect the final blend. In consequence, it enables finding out which ones have the best properties to achieve suitable and speedy pharmaceutical development. Furthermore, it is possible to compare the different manufacturers generally in order to analyse which offers

Table 2
Limit values accepted for the SeDeM Diagram parameters and conversion factor to convert each parameter into radius values (r).

Incidence	Parameter	Limit value (V)	Radius (r)	Factor applied to v
Dimension	Bulk Density	0–1 g/mL	0–10	10v
	Tapped Density	0–1 g/mL	0–10	10v
Compressibility	Inter-particle	0–1.2	0–10	10v/1.2
	Porosity	0–50%	0–10	v/5
	Carr Index	0–200 N	0–10	v/20
	Cohesion Index			
"Flowability"/Powder flow	Hausner Index ratio	3–1	0–10	(30-10v)/2
	Angle of Repose	50–0 (°)	0–10	10-(v/5)
	Powder Flow	20–0 (s)	0–10	10-(v/2)
Lubricity/Stability	Loss on Drying	10–0 (%)	0–10	10-v
	Hygroscopicity	20–0 (%)	0–10	10-(v/2)
Lubricity/Dosage	Particles <50 μm	50–0 (%)	0–10	10-(v/5)
	Homogeneity index	$0–2 \times 10^{-2}$	0–10	(5×10^2)*v

the most suitable products for DC or if they display large differences in IGC values regarding each grade.

2. Materials and methods

The material under study consists of 21 microcrystalline celluloses. They are all listed below: Avicel® 101 Batch 61301C (FMC, Brussels, Belgium), Avicel® 102 Batch 71031C (FMC, Brussels, Belgium), Avicel® 301 Batch P1319C (FMC, Brussels, Belgium), Avicel® 302 Batch Q1243C (FMC, Brussels, Belgium), Avicel® 200 Batch M1401C (FMC, Brussels, Belgium), Comprecel® 101 Batch C0911021-S (Ming Thai Chemical Co., LTD. Taiwan, R.O.C.), Comprecel® 102 Batch C1112039-S (Ming Thai Chemical Co., LTD. Taiwan, R.O.C.), Comprecel® 301 Batch C1408086-S (Ming Thai Chemical Co., LTD. Taiwan, R.O.C.), Comprecel® 302 Batch C1403108-S (Ming Thai Chemical Co., LTD. Taiwan, R.O.C.), Emcocel® 50M Batch 6105050939 (JRS PHARMA GGmbH & Co. KG, Rosenberg, Germany), Emcocel® 90M Batch 6109051321 (JRS Pharma GGmbH & Co. KG, Rosenberg, Germany), Emcocel® 90HD Batch T95063 (JRS Pharma GGmbH & Co. KG, Rosenberg, Germany), Emcocel® 200 LP Batch 256004 (JRS Pharma GGmbH & Co. KG, Rosenberg, Germany), Microcel® 101 Batch 125000004 (Blanver, Farmoquímica, Sao Paulo, Brazil), Microcel® 102 Batch 125001008 (Blanver, Farmoquímica, Sao Paulo, Brazil), Microcel® 200 Batch 1450122014 (Blanver, Farmoquímica, Sao Paulo, Brazil), Vivapur® 101 Batch 6610153224 (JRS Pharma GGmbH & Co. KG, Rosenberg, Germany), Vivapur® 102 Batch 5610201109 (JRS Pharma GGmbH & Co. KG, Rosenberg, Germany), Vivapur® 301 Batch 6630120110 (JRS Pharma GGmbH & Co. KG, Rosenberg, Germany), Vivapur® 302 Batch 5630290339 (JRS Pharma GGmbH & Co. KG, Rosenberg, Germany), Vivapur® 200 Batch 5620011550 (JRS Pharma GGmbH & Co. KG, Rosenberg, Germany).

The procedure for the product characterization of these substances involves determining the 12 parameters of the SeDeM Diagram [19,22]. The methods indicated in the pharmacopoeias were applied wherever possible. When the methods were not available, a system was proposed based on the common practice followed in pharmaceutical research specifically adapted for the SeDeM Diagram [21,30].

3. Experimental results

The parameter values were obtained following the described methodology. Each parameter was determined three times and the mean value was used for radius calculation. Diagram values were calculated by applying the equations in Table 1. The figures obtained were then converted into radii (r) as shown in Table 2. The corresponding parameters and the mean radius values obtained with the samples studied are shown in Table 3 while the SeDeM diagrams are shown in Figs. 1, 2 and 3.

4. Comparison and discussion about the different Microcrystalline Celluloses

The comparison and discussion of Microcrystalline Celluloses is structured around three points. Firstly, the grades are compared for each manufacturer and the results are compared as a whole. Secondly, every MCC is compared against the others of the same grade. That is to say, each manufacturer's product is compared against the others' products. It should be pointed out, that “Compressibility” and “Flowability” incidence means are the most critical functions in SeDeM characterization [29]. They are calculated from eight out of twelve parameters of the conventional SeDeM. Moreover, all of them are involved in the mechanical zone. However, MCCs are classified into grades according to their main functionality and related to their average particle size, as described on the manufacturers' web pages [7–10]. The “Lubricity/Dosage” incidence mean allows us to discern between the different MCCs in this field. Therefore, the sum of “Compressibility” (C), “Flowability” (F) and “Lubricity/Dosage” (L/D) values (see Table 4) is taken into account to analyse the comparison accurately.

Finally, the average of the sum (C + F + L/D) of each grade for each brand is proposed in order to compare the different MCC brands generally (See Table 5).

4.1. Comparison between grades

a. *FMC Biopolymer – Avicel® PH*

In general, all grades of FMC Biopolymer's MCCs displayed an acceptable IGC value. Only grade 101 has an IGC below 5. Grades 102, 302 and 200 show higher IGC values. (See Table 3).

However, there are noticeable differences in the incidence means. As described by the manufacturer, grades 301 and 302 have higher densities (and acceptable “Dimensions” values) than grades 101 and 102, whereas grade 200 has an intermediate value. As far as “Compressibility” is concerned, grade 101 displays the highest “Compressibility” value (8.46). It should be noted that it is the highest value reached among all the MCCs. Grades 102 and 302 show similar values (6.88 and 6.51 respectively), but grade 301 shows rather a lower value (6.02) than grade 101. Grade 200 shows the lowest value (5.39). It therefore seems that the trend followed is: the higher the grade (the larger the particle size), the lower compressibility it displays. This is due to decreasing Ie and IC, since all MCCs have an excellent Icd (see Table 3).

Contrary to its “Compressibility”, grade 200 has the best “Flowability” value, and grades 301 and 302 show similar but higher values than their counterparts (grades 101 and 102) for this incidence mean. There are no notable differences in the values obtained for the “Lubricity/Stability” incidence mean, for which all values are between 6 and 7. MCCs displayed low hygroscopic ability but a high moisture content (% HR).

With regard to the “Lubricity/Dosage” incidence mean, the results are rather heterogeneous. At least 50% of the particles of grades 101 and 301 are below 50 μm, which explains their poor “Flowability”.

Nevertheless, grade 301 displays greater homogeneity as it has even more fine particles than grade 101. Grades 102 and 302 have fewer fine particles but also offer less homogeneity. Grade 302 has a lower “Lubricity/Dosage” value than that of grade 301, and the value of grade 102 is even lower than that of grade 101. As expected, according to the manufacturer's product description, grade 200 has almost no fine particles. It has a poor Homogeneity Index, though it still displays the highest value for this Incidence mean.

On the whole, the SeDeM analysis concludes that grade 101 has the highest compressibility (8.46) but its poor “Flowability” (3.72) and high number of fine particles should be noted. Grade 301 shows a higher density than grade 101 but to the detriment of its “Compressibility”. Grades 102 and 302 show a similar, well-balanced “Compressibility”/“Flowability” ratio. Both incidence means have acceptable values. Grade 200 has an intermediate density and higher “Flowability” but lower “Compressibility” than the other grades.

b. *Ming Thai Chemical – Comprecel®*

IGC values differ regarding grade for Ming Thai Chemical products. Comprecel® 101 and 302 have acceptable IGCs (5.02 and 5.36 respectively), whereas Comprecel® 102 and 301 do not (4.87 and 4.37 respectively) (See Table 3). Likewise, the results obtained regarding the incidence means are more heterogeneous.

It is interesting that there are no differences in “Compressibility” and “Flowability” between grades 101 and 102. Both have similar values for the parameters leading to these Incidence means.

Nevertheless, there are differences regarding “Lubricity/Dosage”. Grade 101 has more fine particles making it more homogeneous (4.13). Grade 102 has a larger particle size (fewer fine particles) and

Table 3
Parameters, incidence means and parametric index.

			SeDeM characterization of DC excipients																			
			Parameters (r)												Mean incidence					Index		
N	*MCC grade*	Excipient	Da	Dc	Ie	IC	Icd	IH	(a)	t″	%HR	%H	%pf	(Iθ)	Dimens	Compressib	Flowabilty	Lub/stability	Lubricity/dosage	IP	IPP	IGC
1	101	Avicel® PH 101 Batch: 61301C	2.81	4.07	9.18	6.19	10.00	7.76	3.41	0.00	3.89	8.04	0.00	6.70	3.44	8.46	3.72	5.97	3.35	0.50	5.17	4.92
2		Comprecel® 101 Batch: C0911021_S	3.54	4.93	6.63	5.64	10.00	8.04	3.11	0.00	4.79	8.33	0.00	8.25	4.24	7.42	3.72	6.56	4.13	0.50	5.27	5.02
3		Microcel® 101 Batch: 125000004	3.14	4.41	7.64	5.76	10.00	7.98	2.02	0.00	3.50	9.15	0.00	8.05	3.78	7.80	3.33	6.33	4.03	0.50	5.14	4.89
4		Vivapur® 101 Batch: 6610153224	3.27	4.22	5.73	4.50	10.00	8.55	3.05	0.00	5.21	7.97	0.00	6.25	3.75	6.75	3.87	6.59	3.13	0.50	4.90	4.66
5		Emcocel® 50 M Batch: 6105050939	3.19	4.09	5.75	4.40	10.00	8.59	2.22	0.00	3.74	8.13	0.00	4.70	3.64	6.72	3.60	5.94	2.35	0.33	4.57	4.35
6	102	Avicel® PH 102 Batch: 71031C	3.35	4.39	5.89	4.74	10.00	8.45	5.11	6.49	4.18	8.36	4.45	3.70	3.87	6.88	6.68	6.27	4.07	0.50	5.76	5.48
7		Comprecel® 102 Batch: C1408086_S	3.38	4.67	6.81	5.52	10.00	8.09	3.23	0.00	5.29	8.08	3.20	3.10	4.03	7.44	3.77	6.68	3.15	0.50	5.11	4.87
8		Microcel® 102 Batch: 125001008	3.29	4.21	5.53	4.37	10.00	8.60	3.33	0.00	3.36	9.20	0.00	1.95	3.75	6.63	3.98	6.28	0.98	0.33	4.49	4.27
9		Vivapur® 102 Batch: 5610201109	3.22	4.28	6.41	4.95	10.00	8.36	3.90	4.17	4.11	8.39	3.23	3.10	3.75	7.12	5.47	6.25	3.17	0.33	5.34	5.09
10		Emcocel® 90 M Batch: 6109051321	3.48	4.32	4.66	3.89	10.00	8.80	4.17	5.17	4.62	7.68	5.04	3.30	3.90	6.18	6.04	6.15	4.17	0.42	5.43	5.17
11	301	Avicel® PH 301 Batch: P1319C	4.55	5.76	3.85	4.20	10.00	8.67	3.66	0.00	5.18	8.13	0.00	10.00	5.16	6.02	4.11	6.65	5.00	0.50	5.33	5.08
12		Comprecel® 301 Batch: C1408086_S	4.37	5.19	3.02	3.16	10.00	9.06	2.57	0.00	5.74	7.92	0.00	4.00	4.78	5.39	3.88	6.83	2.00	0.42	4.59	4.37
13		Vivapur® 301 Batch: 6630120110	4.31	5.71	4.74	4.90	10.00	8.38	4.71	0.00	4.85	8.17	0.00	7.80	5.01	6.55	4.36	6.51	3.90	0.42	5.30	5.04
14	302	Avicel® PH 302 Batch: Q1243C	4.47	5.93	4.59	4.92	10.00	8.37	4.85	7.50	5.50	8.09	3.37	2.95	5.20	6.51	6.91	6.78	3.16	0.50	5.88	5.60
15		Comprecel® 302 Batch:C1403108_S	4.41	5.83	4.60	4.87	10.00	8.39	4.84	5.92	4.27	8.56	3.67	2.25	5.12	6.49	6.38	6.42	2.96	0.42	5.63	5.36
16		Vivapur® 302 Batch: 5630290339	4.21	5.63	4.99	5.04	10.00	8.32	4.10	7.33	5.58	8.09	3.98	4.25	4.92	6.68	6.58	6.83	4.11	0.58	5.96	5.67
17		Emcocel® HD90 Batch: T95063	3.87	4.63	3.53	3.28	10.00	9.02	5.74	8.00	4.70	9.19	5.08	4.10	4.25	5.61	7.59	6.95	4.59	0.50	5.93	5.64
18	200	Avicel® PH 200 Batch: M1401C	3.85	4.52	3.21	2.90	10.00	9.13	5.60	8.08	6.60	7.61	8.28	2.30	4.19	5.39	7.60	7.10	5.29	0.58	6.01	5.72
19		Microcel® 200 Batch: 1450122014	3.76	4.81	4.84	4.37	10.00	8.61	4.72	8.50	4.86	7.76	6.83	3.20	4.29	6.40	7.27	6.31	5.01	0.42	6.02	5.73
20		Vivapur® 200 Batch: 5620011550	3.71	4.62	4.43	3.94	10.00	8.78	5.47	8.06	3.86	8.85	8.00	3.40	4.17	6.12	7.43	6.35	5.70	0.50	6.09	5.80
21		Emcocel® 200LP Batch: 256004	3.12	3.80	4.78	3.58	10.00	8.91	5.44	7.17	4.39	8.97	7.86	1.35	3.46	6.12	7.17	6.68	4.60	0.50	5.78	5.50

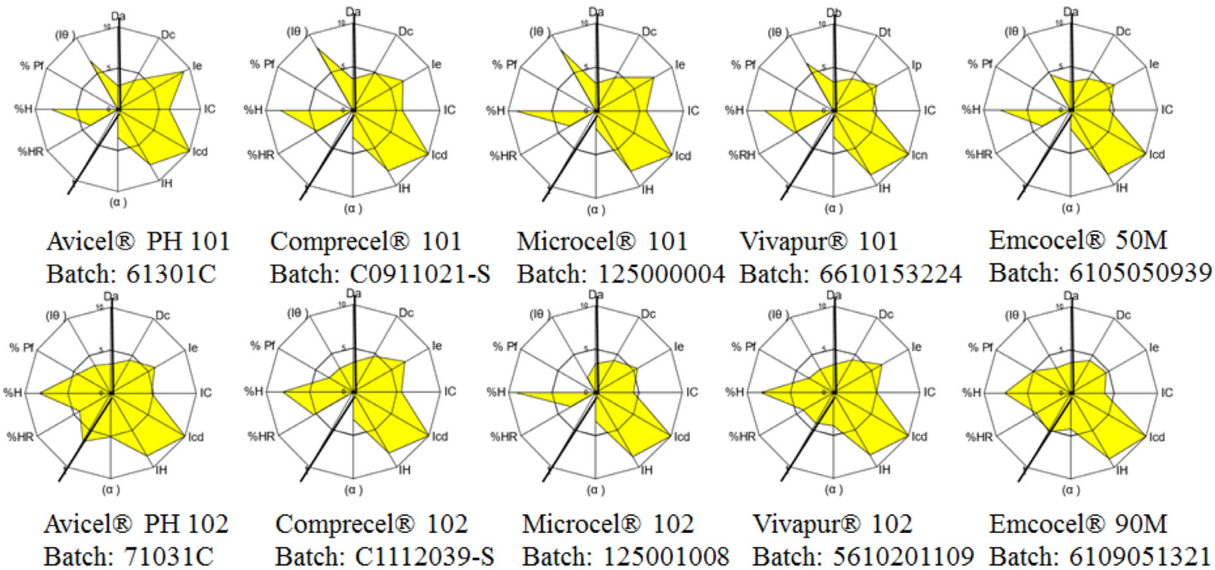

Fig. 1. SeDeM diagrams obtained for grades 101 and 102.

less homogeneity (3.15). In any case, it should be noted that in this case, both grades show the same behaviour for "Compressibility"/ Flowability", regardless of the different particle size.

Another point to highlight is the comparison between grades 101 and 301. Grade 301 does not show a major increase in the "Dimensions" value, although the dimensions of Comprecel® 101 are already higher than the other grade 101 MCCs. Besides, there is no improvement in "Flowability" terms while there is a real decrease in the "Compressibility" value. The "Lubricity/Dosage" incidence mean is also lower for grade 301 (2.00) due to a decrease in homogeneity. When the comparison of grade 301 against grade 101 is analysed, it is clear that in fact grade 301 is less suitable for DC than grade 101 because its slightly increased dimensions do not offset the decrease in incidence means.

However, grade 302 displays higher "Dimensions" and lower "Compressibility" values than grade 102 but well-balanced "Compressibility"/"Flowability". There are no differences between them in terms of "Lubricity/Stability" and "Lubricity/Dosage". Therefore, we can conclude that the improved "Flowability" and "Dimensions" of grade 302 compensate for its low "Compressibility" and as a result, it has a higher IGC.

To sum up, apart from particle size, there are no differences between grades 101 and 102 produced by Ming Thai Chemical in regard to their suitability for DC. The analysis also concludes that grade 302 is more suitable than grade 102 for DC whereas grade 301 is less so.

c. *Blanver – Microcel®*

IGCs for Blanver's grades 101 and 102 are below the acceptability limit but grade 200 has one of the highest IGC values. Grade 102's IGC is lower than 101's IGC, meaning that Microcel® 102 is less suitable for direct compression than Microcel® 101.

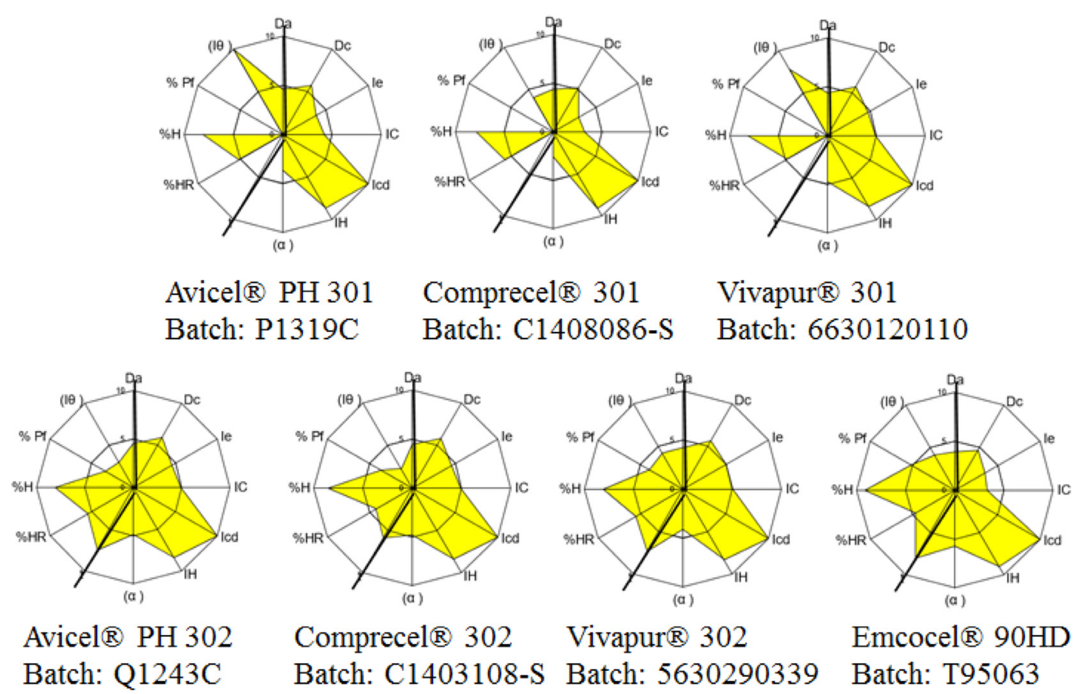

Fig. 2. SeDeM diagrams obtained for grades 301 and 302.

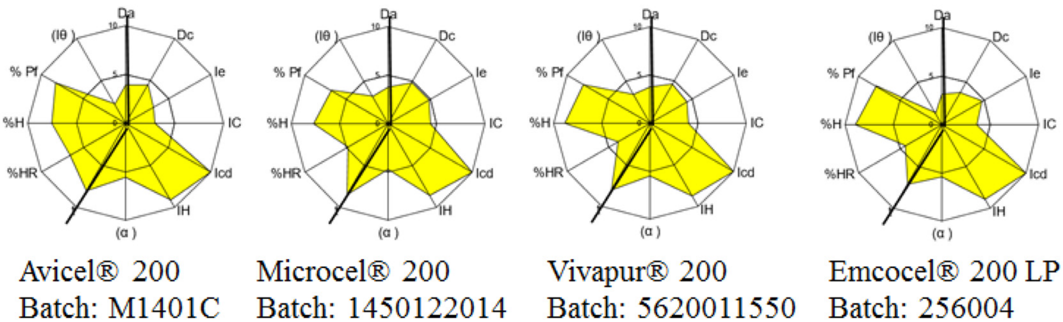

Fig. 3. SeDeM diagrams obtained for grade 200.

The characterization shows that there are no differences between grades 101 and 102 concerning the “Dimensions” incidence mean. Both are deficient values due to the low MCC density. However, grade 101 has a higher “Compressibility” value (7.80) than grade 102 (6.63), as described above in the comparison of Avicel®, owing to a decrease in IC and Ie. Despite the “Compressibility” decrease, grade 102 only shows slightly higher “Flowability”. Furthermore, like grade 101, this grade has a high number of fine particles (> 50%) and a low Homogeneity Index. Therefore, it has a lower “Lubricity/Dosage” incidence mean.

These results were unexpected since the manufacturer suggests the use of grade 102 for direct compression and grade 101 for wet granulation.

Table 4
Sum of “Compressibility”, “Flowability” and “Lubricity/Dosage”.

N	Excipient	Sum (C + F + L/D)
1	Avicel® PH 101 Batch: 61301C	15.53
2	Comprecel® 101 Batch: C0911021_S	15.27
3	Microcel® 101 Batch: 125000004	15.16
4	Vivapur® 101 Batch: 6610153224	13.75
5	Emcocel® 50 M Batch: 6105050939	12.67
6	Avicel® PH 102 Batch: 71031C	17.63
7	Comprecel® 102 Batch: C1408086_S	11.36
8	Microcel® 102 Batch: 125001008	11.59
9	Vivapur® 102 Batch: 5610201109	15.76
10	Emcocel® 90 M Batch: 6109051321	16.39
11	Avicel® PH 301 Batch: P1319C	15.13
12	Comprecel® 301 Batch: C1408086_S	11.27
13	Vivapur® 301 Batch: 6630120110	14.81
14	Avicel® PH 302 Batch: Q1243C	16.58
15	Comprecel® 302 Batch:C1403108_S	15.83
16	Vivapur® 302 Batch: 5630290339	17.37
17	Emcocel® HD90 Batch: T95063	17.79
18	Avicel® PH 200 Batch: M1401C	18.28
19	Microcel® 200 Batch: 1450122014	18.68
20	Vivapur® 200 Batch: 5620011550	19.25
21	Emcocel® 200LP Batch: 256004	17.89

Microcel® 200 has a higher “Dimensions” value and its “Compressibility” (6.40) is similar to but slightly lower than Microcel® 102's “Compressibility” (6.63). Due to its larger particle size, Microcel® 200 displays adequate “Flowability” (7.27). It flows freely thorough a funnel whereas the other grades do not.

As far as “Lubricity/Dosage” (5.01) is concerned, grade 200 shows a low value for the Homogeneity Index (3.20) yet it shows a low percentage of fine particles, as was expected (6.83). The results obtained for “Lubricity/Stability” (6.31) are quite similar to grades 101 (6.33) and 102 (6.28), although it has a lower moisture content but it is slightly more hygroscopic.

To conclude, the main differences between Microcel® 101 and Microcel® 102 are lower “Compressibility” and “Lubricity/Dosage” to achieve slightly better “Flowability”. As a result, grade 102, which does not fulfil the manufacturer's description, is less suitable for DC. Grade 200, with its larger particle size, has adequate “Flowability” and preserves decent “Compressibility”. It has the highest IGC of these three products.

d. *JRS – Vivapur® and Emcocel®*

As described above, JRS produces MCCs via two different techniques. Regarding this, the different grades of Vivapur® are compared as well as those of Emcocel®. Secondly, the differences between Vivapur® (air stream manufacture) and Emcocel® (spray-dried manufacture) are analysed for each grade.

All grades of Vivapur® have an acceptable IGC, except Vivapur® 101 (4.66). Vivapur® 102 (5.09) and Vivapur® 301 (5.04) have similar IGCs whereas Vivapur® 302 (5.67) and Vivapur® 200 (5.80) present the highest IGC values.

This brand's grades 301 and 302 have greater densities (5.01 and 4.92 respectively) than grades 101 and 102 (both 3.75) with the “Dimensions” value near to the acceptance limit. The intermediate value (4.17) of grade 200 is slightly higher than grades 101 and 102.

Vivapur® 102 displays a higher “Compressibility” value (7.12) than Vivapur® 101 (6.75) due to higher values in Ie and IC. Vivapur® is the only brand whose grade 102 displays better “Compressibility” than its grade 101. Vivapur® 102 also shows improved “Flowability” with an

Table 5
Average IGC and Sum (C + F + L/D) values for each brand.

Manufacturer	MCC brand	Average of Sum (C + F+ L/D)	Average of IGCs	SD[a] of IGC average	CV[b] (%) of IGCs average
FMC Biopolymer	Avicel® PH	16.63	5.36	0.34	6.42
Ming Thai	Comprecel®	13.43	4.91	0.41	8.39
Blanver	Microcel®	15.14	4.96	0.73	14.76
JRS	Vivapur®	16.19	5.25	0.46	8.89
JRS	Emcocel®	16.19	5.14	0.57	11.24

[a] SD means standard deviation.
[b] CV means coefficient of variation.

acceptable value (5.48), whereas Vivapur® 101 (3.81 "Flowability" value) does not flow freely thorough a funnel and displays a worse angle of repose. There are also differences in "Lubricity/Dosage", while the incidence mean values are closer. Vivapur® 101 has a large amount of fine particles but provide homogeneity. However, Vivapur® 102 has fewer fine particles although it is less homogeneous. Thus, Vivapur® 102 is more suitable for DC than Vivapur® 101.

Vivapur® 301 and 302 have greater densities than their counterparts, so they have higher "Dimensions" values. Both display lower "Compressibility" than their counterparts but higher "Flowability". These differences are slightly more noticeable in grade 302. Vivapur® 301 is more homogeneous than Vivapur® 101, and Vivapur® 302 has fewer fine particles than Vivapur® 102 and is more homogeneous. Therefore, Vivapur®'s grades 301 and 302 result in better grades than their counterparts, where the improved incidence means change the "Compressibility" deficit into a favourable scenario.

Vivapur® 200 displays the highest "Flowability" but reduced "Compressibility" due to its larger particle size. As explained previously, a larger particle size is related to higher powder flow but less "Compressibility". Vivapur 200 is not homogeneous but it has few fine particles and, as a result, it displays acceptable "Lubricity/Dosage" (5.70).

Emcocel® also displays acceptable IGCs for all grades, except for grade 50 M (equivalent to grade 101 particle size).

Characterization identifies some differences between Emcocel® 50 M and Emcocel® 90 M (equivalent to grade 102). The same trend described for Vivapur® is seen again. The grade of larger particle size displays less "Compressibility" but rather enhanced "Flowability". Another difference that should be highlighted is that it shows the same homogeneity as Vivapur® 102 but has fewer fine particles (< 25%). Therefore, the "Lubricity/Dosage" incidence mean is better.

Nonetheless, there are no noticeable differences concerning "Dimensions" and "Lubricity/Stability".

Emcocel® 50 M produces a similar SeDeM diagram to Vivapur® 101 although all of its mean incidence values are lower than those of Vivapur® 101. The greatest difference is seen for "Lubricity/Dosage" owing to the low homogeneity of Emcocel® 50 M. Thus, it has a lower IGC than Vivapur® 102.

Emcocel® 90 M displays less "Compressibility" but higher "Flowability" than Vivapur® 102. It shows a decrease of Ie and IC but increased flow time and angle of repose. As described above, it displays higher "Lubricity/Dosage" (4.17 vs 3.17). In consequence, Emcocel® 90 M has a slightly higher IGC than Vivapur® 102.

Emcocel® HD90 (equivalent to grade 302) has a higher IGC than Emcocel® 90 M (5.64 vs 5.17), although its density is not so increased and its "Compressibility" is even more reduced. This means that its "Flowability" is somewhat improved. In fact, it has the highest "Flowability" in this grade and, as described for Emcocel® 90 M, it has fewer fine particles (< 25%). In comparison with Vivapur® 302, the lower "Dimensions" and "Compressibility" of Emcocel® HD90 are offset by its high "Flowability" and higher "Lubricity/Dosage", which result in a similar IGC.

Finally, Emcocel® LP 200 has a lower but similar IGC to the other MCCs of this grade (5.50). Whereas these incidence means ("Compressibility", "Flowability" and "Lubricity/Stability") are similar to the others, there are differences regarding "Dimensions" and "Lubricity/Dosage". It has lower "Dimensions" than the other MCCs. Indeed, its density is equivalent to grade 101 (3.46). Similarly, it is less homogeneous than Vivapur® 200. These two lower incidence means result in a lower IGC.

To sum up, there are differences between Vivapur®'s grades and they have been well characterized. For this brand, grade 102 offers better "Compressibility" and better "Flowability" than grade 101. Grades 301 and 302 show an improvement concerning their counterparts. The reduced "Compressibility" is offset by an improvement in the other incidence means. Vivapur® 200 has the highest IGC because it combines high "Flowability" and acceptable "Compressibility". However, there are no major differences between Emcocel® and Vivapur®. For grades 101 and 200, Emcocel® is simply less suitable for DC compression than Vivapur®. Grades 102 and 302 show similar IGCs, but Emcocel® displays higher "Flowability" but lower "Compressibility".

e. *General discussion*

Finally, the comparisons of the manufacturers' products described above are compared to each other.

Regarding the results described, it is clear that there are differences between the manufacturers' different grades. The differences between grades are well defined for the products of FMC Biopolymer and JRS, whereas there are no differences between grades 101 and 102 for Ming Thai's products (other than particle size), and grade 301 was less suitable for DC than grade 101. With regard to Blanver's products, grade 102 was less suitable for DC than grade 101, which would disagree with its product description. It even has a large number of fine particles, like grade 101 (> 50%).

The two products offered by JRS (Emcocel® and Vivapur®) are not different for any grade. Only grades 102/90 M and 302/90HD differ from each other whereas grades 50 M and 200LP only have lower IGCs than grades 101 and 200.

4.2. Comparison between manufacturers

Although the differences between each grade have been described for each manufacturer and compared in general terms, each MCC of the same grade may vary greatly. These differences are now described below.

a. *Grade 101*

The IGC values of Avicel® PH, Microcel® and Comprecel® are close to the acceptable limit value, whereas Vivapur®'s IGC value is lower. This is due to the fact that Vivapur® displays a lower compressibility value than the others.

All MCCs have an excellent cohesion (Icd) parameter (10.00). However, Avicel® PH 101 is the only one whose "Compressibility" incidence is higher than 8.00. This is because it also has an excellent Ie (see Table 3). Regarding "Flowability", none flows freely through a funnel. In spite of this poor flowability, all of them provide a good Hausner's Index value. Another difference described between them is that only Vivapur® has a moisture content lower than 5%.

There are also differences in "Lubricity/Dosage" incidence mean. Comprecel® and Microcel® show the highest values whereas Emcocel® shows the lowest. These differences are due to the Homogeneity index. Despite the high value of fine particles shown by all MCCs, there are differences in their particle size distribution. The high amount of fine particles explains the poor rheology but it grants some homogeneity to the product. Although Avicel® PH 101 does not have the best IGC, it achieves the best sum (C + F + L/D) for this grade, whereas Vivapur® 101 and Emcocel® 50 have the lowest sums.

If the results are analysed, Vivapur®'s properties are less suitable for compression by DC than the other MCCs.

b. *Grade 102*

There are significant differences in the MCCs that belong to this grade. Avicel® PH 102 displays the highest IGC (5.48), whereas Microcel® 102 displays the lowest IGC (4.27), and a huge distance separates them ($\Delta = +1.21$). In contrast, Vivapur® 102 and Emcocel® 90 M show similar IGC values (5.09 and 5.17 respectively). Comprecel® 102 (4.87) does not reach the acceptable limit either.

If we analyse the Incidence Means, no MCCs reach the acceptable "Dimensions" value. "Compressibility" is lower than for grade 101, except for Vivapur 102. In this case, Comprecel® 102 and Vivapur® 102 (7.44 and 7.12 respectively) have the highest values, and Emcocel® has the lowest value (6.18). All MCCs display excellent cohesion and so "Compressibility" differences are due to different IC and Ie.

The largest differences are observed are for mean "Flowability". Whereas Avicel® PH 102 (6.68), Emcocel® 90 M (6.04) and Vivapur® 102 (5.47) have acceptable values, Comprecel® 102 (3.77) and Microcel® 102 (3.94) have values below 4. Moreover, these two products do not flow freely.

There are also differences in "Lubricity/Dosage", but in this case, neither of them reaches an acceptable value. Microcel® 102 shows the lowest value because it has a large number of fine particles and low homogeneity (as described above). Comprecel® 102 and Vivapur® 102 have similar incidence mean values as well as similar parameter values. Avicel® PH 102 and Emcocel® 90 M have similar homogeneity values to Comprecel® 102 and Vivapur® 102, but different amounts of fine particles. Thus, it is possible to conclude that even if they are the same product, the particle size distribution of each brand is different.

c. *Grade 301*

The MCCs that belong to grade 301 should have the same particle size and quality but improved "Dimensions" and in some cases enhanced "Flowability".

The "Dimensions" are increased for all MCCs of this grade. As a result, Comprecel® 301 and Avicel® 301 show a decrease in "Compressibility" in comparison with their counterparts. Vivapur® 301 shows similar "Compressibility" to Vivapur® 101, but it should be taken into account that Vivapur® 101 has lower "Compressibility" than the other 101 MCCs.

In terms of "Flowability", Avicel® PH 301 and Vivapur® 301 have higher values than their counterparts. Contrary to this, Comprecel® 301 does not show any improvement because its "Compressibility" and its "Lubricity/Dosage" are reduced and there is no real "Flowability" improvement. The sum of (C + F + L/D) is higher for the Vivapur® and Avicel® brands than for the Comprecel® brand in this grade. Moreover, the sum of (C + F + L/D) for Avicel® PH 301 (15.13) is similar to Avicel® PH 101 (15.53), whereas Comprecel® 301 (11.27) is somewhat lower than its 101 (15.27) counterpart. Only Vivapur® 301 shows a higher value (14.81).

In relation to the "Lubricity/Dosage" incidence mean, they contain large amounts of fine particles (all above 50%). Then, the differences arise from the different Homogeneity Index. Avicel® PH 301 has an excellent Homogeneity Index (10.00) and Vivapur® 301 also shows improved homogeneity (7.80) versus Vivapur® 101 (6.25). However, Comprecel® 301 shows the lowest Homogeneity Index (4.00) and is lower than the Index for Comprecel® 101 (8.25).

To sum up, Vivapur® 301 shows an improvement against Vivapur® 101 as well as Avicel® PH 301, but the latter shows a critical "Compressibility" decrease. Conversely, Comprecel® 301's properties are less suitable for direct compression than Comprecel® 101's properties. However, it should be taken into account that Vivapur® 101 has the lowest IGC.

d. *Grade 302*

All Grade 302 MCCs have an acceptable IGC (around 5.60) but Comprecel® 302 displays the lowest IGC (5.36).

The "Dimensions" values are acceptable or close to acceptable for this grade, except for Emcocel® HD90. Emcocel® HD90 also displays the lowest "Compressibility" value, around one unit from the others. The values obtained for "Flowability" are very similar to the values for "Compressibility".

All grade 302 MCCs display "Lubricity/Dosage" values below the acceptable limit, but Vivapur® 302 (4.11) and Emcocel® HD90 (4.59) display higher values than Comprecel® 302 (2.96) and Avicel® PH 302 (3.16). In this grade, differences between them are found in the number of fine particles and the homogeneity index. Emcocel® HD90 and Vivapur® 302 show better "Lubricity/Dosage" than grade 102. However, Comprecel® 302 and Avicel® PH 302 show lower values concerning this incidence mean.Therefore, the sums of (C + F + L/D) obtain dissimilar values. Emcocel® HD 90 (17.79) and Vivapur® 302 (17.37) have higher values, which are closer to Avicel® PH 102 (17.63). However, Avicel® PH 302 (16.58) displays a lower value than its counterparts. It should be noted that FMC Biopolymer describes Avicel® PH 302 only as a high density MCC, but not as an MCC with improved flow. That is to say, it fulfils the manufacturer's description. Comprecel® 302 has the lowest sum of (C + F + L/D) for this grade (15.83).

e. *Grade 200*

Avicel® PH 200 (5.72), Microcel® 200 (5.73) and Vivapur® 200 (5.80) show adequate and higher IGCs than Emcocel® 200LP (5.50).

The same products show "Dimensions" values that are higher than and similar to Emcocel®'s "Dimensions" value, but all of them are below 5. However, all grade 200 MCCs display adequate "Compressibility" values, but it is Avicel® PH 200 (5.39) that has the lowest value with a $\Delta = -1.01$ lower than the highest (Microcel® 200) (6.40). As far as "Flowability" is concerned, all MCCs have excellent values for Hausner's index and flow time.

In contrast to the other grades, Grade 200 has acceptable values for "Lubricity/ Dosage" (5.01 to 5.70) except for Emcocel® 200LP (4.60). In spite of the low homogeneity displayed by this grade, it has a low quantity of fine particles which provides it with good fine particle values. Vivapur® displays the best value for this incidence mean. Not only does it achieve the best sum of (C + F + L/D) in this grade, but it is also the highest value for all grades (19.25).

f. *MCC brands' Sum (C + F + L/D) and IGC averages*

The average IGC and the average sum of (C + F + L/D) reflect the trend followed for each brand, and the results show that there are general differences between each brand.

FMC Biopolymer and JRS obtain an adequate overall IGC average (value higher than 5) for their products. However, Blanver and Ming Thai display unacceptable overall IGCs, although they are close to 5. The difference is larger in the average of the sum (C + F + L/D) where JRS and FMC Biopolymers's brands have higher values than the other brands.

Furthermore, Comprecel® displays the lowest value for both averages, whereas Avicel® displays the highest values for both averages and the lowest IGC coefficient of variation, which means that all of its MCCs have similar IGCs. Blanver displays a coefficient of variation two times higher than Avicel® because some of its MCCs have a high IGC value (Microcel® 200), whereas others (Microcel® 102) display the lowest IGC.

A low CV with a good IGC value point to a reliable manufacturing technique where the different grades may display different incidence mean values, but they have the same overall quality or suitability for direct compression. A high CV means that not only are there differences in the incidence means but they also have different final product qualities.

5. Conclusions

- The SeDeM diagram allows characterizing powders and, consequently, accurately comparing them.
- Differences for each grade are well defined by JRS and FMC Biopolymer.
- There are no differences between Ming Thai's grades.
- Blanver's grade 102 does not meet the manufacturer's description (it is less suitable for DC than the grade 101).
- Grades 200 and 302 are the most suitable for DC.
- Grade 101 displays the highest "Compressibility" but the lowest "Flowability".
- JRS and FMC Biopolymer tend to display higher IGCs for their products than Blanver and Ming Tai.
- Grade 200 displays a well-balanced ratio between Compressibility

and Flowability as well as acceptable values for "Lubricity/Dosage".

- Ming Thai has the lowest values in both averages (Sum of C + F + D/L and IGC).
- FMC Biopolymer shows the highest overall values and the lowest CV (%).

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