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Research paper

The use of the SeDeM Diagram expert system to determine the suitability of diluents–disintegrants for direct compression and their use in formulation of ODT

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ABSTRACT

The new SeDeM Diagram expert system was used to analyze the suitability of 43 excipients for direct compression with disintegrant properties from eight chemical families. The SeDeM Diagram expert system is a new method for use in tablet preformulation and formulation studies. It provides the profile of a substance in powder form in terms of its suitability for direct compression.

This study, which was based on the current concept of "Quality by Design ICH Q8", evaluated the pharmacotechnical properties of disintegrants in powder form and selected the candidates that were most suitable for direct compression and their use in formulation of orally disintegrating tablets (ODT). To achieve this, each disintegrant and its chemical families were individually analyzed. It was concluded that nine disintegrants had an SeDeM value with the index of good compression (IGC) over 5. Most of these disintegrants were from the microcellulose family. Other disintegrants had indexes that were close to 5. It is assumed that these excipients can be used in direct compression, when they are added to other excipients.

1. Introduction

In recent years, there has been a sharp increase in the number of orally disintegrating tablets (ODT) available on the market, such as mouth-dissolving tablets. An ODT is generally in a solid dosage form and contains a medicinal substance that disintegrates rapidly and dissolves in the mouth without water within 180 s or less. ODTs are also known as quick dissolve, fast melt, fast dissolving, rapid dissolve, or orally dissolving tablets. The European Pharmacopoeia defines ODTs as orodispersible tablets or tablets intended to be placed in the mouth, which subsequently disperse rapidly before being swallowed [1]. These products have increased in popularity as old and young consumers find them convenient and easy to use. In addition, pharmaceutical companies have extended product life cycles [2] or differentiated their products by offering new dosage forms [3]. Several technologies are available for manufacturing orally disintegrating tablets [1]. The most common preparation methods are molding, lyophilization, freeze-drying, and direct compression. Other methods include cotton candy and spray drying [4]. Each method has advantages and disadvantages. For example, although lyophilization produces tablets that disintegrate very fast (<5 s), they are often less robust and usually require special packaging. Direct compression is a commonly used tablet manufacturing process to produce ODTs. As this method uses existing high-speed tablet presses and common excipients, it is often favored over other manufacturing processes for orally disintegrating tablets. A direct compression formulation has better physical properties than other methods and may eliminate the need for special packaging such as blister packs [3]. A direct compressed orally disintegrating tablet formulation (mouth dissolving) usually contains diluent, disintegrant, lubricant, flow aid, flavor, sweetener, and often color. To achieve rapid disintegration, direct compression ODT formulations typically contain high levels of a superdisintegrant. Depending on the level and characteristics of the active pharmaceutical ingredient (API) and the desired release profile, the levels of disintegrant used can be 10–20 wt.% of the formulation and may be higher or lower in some cases. Thus, it is essential to choose the optimal disintegrant when an ODT formulation is developed. As with most direct compression formulations, additional excipients have to be added such as a suitable flow aid and a lubricant for the tablet manufacture. As ODTs dissolve in the mouth, they often include flavors and sweeteners to mask the taste of bitter active ingredients. Finally, color may be added to the formulation for aesthetic reasons and to aid the identification of the final dosage form [5].

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Table 1
Test results of excipients divided in parameters required by the SeDeM expert system.

Excipient	Composition	Parameters (radius)												Incidence					
		Da	Dc	Ie	IC	Icd	IH	(α)	t''	%HR	%H	%Pf	($I\theta$)	Dimension	Compression	Flowability/ powder flow	Lubricity/ stability	Lubricity/ dosage	IGC
Avicel®101 Lot 6410C	Microcrystalline cellulose FMC Corp/ USA	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	**5.04**
Avicel®102 Lot 7201C	Microcrystalline cellulose FMC Corp/ USA	3.73	5.05	5.83	5.22	10.00	5.49	3.90	0.00	2.76	8.48	4.48	3.75	4.39	7.02	3.13	5.62	4.12	4.66
Avicel®112 Lot 9232C	Microcrystalline cellulose FMC Corp/ USA	3.52	4.77	6.19	5.23	10.00	5.49	4.92	1.00	4.91	7.50	6.02	3.65	4.14	7.14	3.80	6.21	4.84	**5.01**
Avicel®200 Lot M343C	Microcrystalline cellulose FMC Corp/ USA	3.88	4.91	4.49	4.18	10.00	5.79	6.30	6.61	4.75	7.47	8.31	2.10	4.39	6.22	6.23	6.11	5.20	**5.46**
Emcocel®50M Lot 550600	Microcrystalline cellulose Penwest Pharmaceutical/USA	3.10	4.73	9.25	6.88	9.16	4.92	2.79	0.00	2.79	9.35	0.80	7.85	3.91	8.43	2.57	6.07	4.33	4.89
Emcocel®90M Lot 959134	Microcrystalline cellulose Penwest Pharmaceutical/USA	3.40	4.77	7.04	5.74	10.00	5.32	4.70	3.20	3.41	8.22	0.00	3.30	4.09	7.59	4.40	5.82	1.65	4.69
MCC®50M Lot 550600	Microcrystalline cellulose Penwest Pharmaceutical/USA	3.10	4.73	9.25	6.88	9.16	4.92	2.79	0.00	2.79	9.35	0.80	7.85	3.91	8.43	2.57	6.07	4.33	4.89
MCCSannaq®101 Lot 141203	Microcrystalline cellulose Pharmatrans Sanaq/Switzerland	2.80	4.38	10.00	7.20	1.61	4.79	0.00	0.00	2.45	8.54	0.00	10.00	3.59	6.27	1.60	5.49	5.00	4.11
MCCSannaq®102 Lot 241203	Microcrystalline cellulose Pharmatrans Sanaq/Switzerland	3.26	5.09	9.20	7.20	6.80	4.79	1.11	0.00	2.79	8.47	2.20	2.45	4.18	7.73	1.97	5.63	2.33	4.23
MCCSannaq®200L Lot 941204	Microcrystalline cellulose Pharmatrans Sanaq/Switzerland	3.76	5.22	6.20	5.59	*10.00*	5.37	2.59	0.00	2.79	9.24	5.20	1.65	4.49	7.26	2.65	6.02	3.43	4.57
MCCSannaq®UL-002 Lot 40410	Microcrystalline cellulose Pharmatrans Sanaq/Switzerland	2.36	3.81	10.00	7.61	1.24	4.62	0.91	0.00	2.29	9.04	0.00	8.70	3.09	6.28	1.84	5.67	4.35	4.01
Microcel®MC 101 Lot 1960/ 4	Microcrystalline cellulose Blanver/Brasil	2.99	4.59	9.72	6.97	10.00	4.88	2.93	0.00	2.80	7.97	0.00	9.75	3.79	8.90	2.60	5.38	4.88	4.97
Microcel®MC 102 Lot 1960/ 4	Microcrystalline cellulose Blanver/Brasil	3.40	4.50	5.99	4.89	7.59	5.59	3.95	0.00	3.20	9.10	3.80	8.15	3.95	6.16	3.18	6.15	5.98	4.77
Microcel®MC 250 Lot 1960/ 4	Microcrystalline cellulose Blanver/Brasil	4.06	5.62	5.70	5.55	10.00	5.39	4.87	8.50	2.97	8.48	6.80	1.75	4.84	7.08	6.25	5.73	4.28	**5.53**
Vivapur®101 Lot 6610152949	Microcrystalline cellulose JRS/Germany	3.06	4.81	9.91	7.28	10.00	4.76	4.05	0.00	3.79	6.74	0.00	8.15	3.94	9.06	2.94	5.26	4.08	4.96
Vivapur®102 Lot 5610264136	Microcrystalline cellulose JRS/Germany	3.32	5.28	9.32	7.42	10.00	4.70	3.44	1.50	3.90	7.59	3.46	3.05	4.30	8.91	3.21	5.75	3.26	**5.00**
Vivapur®12 Lot 6601260202	Microcrystalline cellulose JRS/Germany	3.62	5.38	7.53	6.54	10.00	5.05	4.47	7.00	3.89	6.19	5.30	2.70	4.50	8.02	5.51	5.04	4.00	**5.37**
Vivapur®200 Lot 560061239	Microcrystalline cellulose 200 JRS/ Germany	3.70	4.79	5.13	4.55	10.00	5.68	4.64	5.17	4.07	8.14	9.20	2.65	4.25	6.56	5.16	6.11	5.93	**5.37**
Prosolv®HD90 Lot K950044	Microcrystalline cellulose + SI O2 Penwest Pharmaceutical/USA	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	**5.94**
Pharmaburst®C1 Lot 04K111	Manitol + St1500 + crosp + croscarm + SI O2 SPI Pharma/UK	4.50	5.62	3.69	3.99	10.00	5.84	6.49	7.25	5.70	6.72	6.20	3.65	5.06	5.89	6.53	6.21	4.93	**5.52**
Aquasorb®A500 Lot 51514	Sodium carboxymethylcellulose HERCULES/Netherlands	4.46	6.33	5.50	5.89	7.24	5.27	0.00	0.00	3.14	2.16	8.38	9.95	5.40	6.21	1.76	2.65	9.16	4.60
Cekol®30,000A Lot NNP53812	Sodium carboxymethylcellulose HERCULES/Netherlands	5.69	7.71	3.83	5.23	1.19	5.49	0.00	0.00	1.90	0.00	0.00	2.45	6.70	3.41	1.83	0.95	1.23	2.66
Nymcel®ZSB16 Lot NN1C2152	Sodium carboxymethylcellulose HERCULES/Netherlands	5.05	7.41	5.25	6.36	6.94	5.11	0.00	0.00	4.34	4.81	0.00	6.55	6.23	6.18	1.70	4.58	3.28	4.11
Nymcel®ZSB-10 Lot NN1C2851	Sodium carboxymethylcellulose HERCULES/Netherlands	3.80	5.89	7.82	7.12	7.53	4.82	0.00	0.00	1.60	2.79	0.00	10.00	4.84	7.49	1.61	2.19	5.00	4.08
Nymcel®ZSD-16 Lot NN143051	Sodium carboxymethylcellulose HERCULES/Netherlands	5.00	7.26	5.19	6.23	10.00	5.16	0.00	0.00	4.42	4.71	0.00	10.00	6.13	7.14	1.72	4.57	5.00	4.60
Nymcel®ZSX Lot NN152551	Sodium carboxymethylcellulose HERCULES/Netherlands	6.42	8.34	3.00	4.62	0.59	5.67	0.00	0.00	5.44	1.90	8.22	10.00	7.38	2.73	1.89	3.67	9.11	4.30

(*continued on next page*)

Table 1 (*continued*)

Excipient	Composition	Parameters (radius)												Incidence					
		Da	Dc	Ie	IC	Icd	IH	(α)	t''	%HR	%H	%Pf	($I\theta$)	Dimension	Compression	Flowability/ powder flow	Lubricity/ stability	Lubricity/ dosage	IGC
Nymcel®ZSX-W Lot NN144050	Sodium carboxymethylcellulose HERCULES/Netherlands	5.38	8.20	5.33	6.88	5.16	4.92	0.00	0.00	3.74	2.79	0.00	10.00	6.79	5.79	1.64	3.26	5.00	4.16
Corn starch B®Lot 385-124	Maize starch ROQUETTE/France	5.76	7.16	2.83	3.91	2.53	5.86	0.00	0.00	0.00	8.99	0.00	8.10	6.46	3.09	1.95	4.49	4.05	3.58
Starch®1500 Lot ref4220	Pregelatinized starch Colorcon/Spain	6.18	8.07	3.16	4.69	5.46	5.65	7.11	0.75	0.00	8.74	3.01	7.45	7.13	4.44	4.50	4.37	5.23	4.78
Lycatab®C Lot 05-GU-235	Partially pregelatinized maize starch ROQUETTE/France	6.69	8.09	2.16	3.47	4.30	5.97	0.00	0.20	2.47	7.62	6.49	3.50	7.39	3.31	2.06	5.04	4.99	4.04
Fecula®NP Supra Bact Lot A394	Maize starch NP = supra bacteriological grade ROQUETTE/France	6.77	7.95	1.83	2.97	7.97	6.08	0.00	0.00	0.00	9.56	0.00	4.60	7.36	4.26	2.03	4.78	2.30	3.79
Plasdone®S630 Lot 6272473	Copovidone BASF/Germany	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	4.60
Kollidon®VA 64 fine Lot 55470188QO	Crospovidone BASF/Germany	0.97	1.87	10.00	9.63	0.00	3.57	0.00	0.00	3.62	2.42	9.60	9.60	1.42	6.54	1.19	3.02	9.60	4.07
Kollidon®CL Lot 91861609T0 Poliplasdone®XL	Crospovidone BASF/Germany	3.91	4.90	4.33	4.06	8.72	5.82	0.00	4.55	2.94	0.00	4.95	3.55	4.40	5.71	3.46	1.47	4.25	3.79
Lot 03500142748	Crospovidone ISP/USA	3.02	3.95	6.49	4.70	8.05	5.64	0.00	8.34	5.00	0.00	6.50	2.75	3.48	6.41	4.66	2.50	4.63	4.32
Poliplasdone®XL-10 Lot 03500129655	Crospovidone ISP/USA	3.85	5.21	5.67	5.23	10.00	5.49	10.00	0.00	5.30	0.00	0.00	10.00	4.53	6.97	5.16	2.65	5.00	4.82
Rxcipients®FM 1000 Lot 195107	Calcium silicate J.M. HUBERT/Belgium	5.79	9.30	5.43	7.54	0.22	4.65	0.00	0.00	0.00	10.00	8.96	4.50	7.55	4.40	1.55	5.00	6.73	4.47
Veegum®Lot 9E609	Magnesium aluminium silicate type IB R.T. VANDERBILT Co./USA	4.74	6.05	3.82	4.34	0.52	5.74	0.00	0.00	1.49	7.62	9.78	6.00	5.39	2.89	1.91	4.55	7.89	3.97
Brenncel-DIS®Lot 93090118	Sodium starch glycolate BRENNTAG/ Spain	9.26	10.00	1.67	3.70	0.46	5.91	0.00	3.45	2.90	10.00	9.80	4.60	9.63	1.94	3.12	6.45	7.20	4.90
Glycolys®Lot E0688	Sodium starch glycolate ROQUETTE/ France	8.94	9.81	0.83	1.79	0.32	6.34	0.00	9.42	4.31	2.08	0.00	10.00	9.38	0.98	5.25	3.19	5.00	4.27
Alginic Acid®DC Lot 560811	Alginic acid ISP/USA	6.07	7.59	2.74	4.00	0.92	5.83	0.00	0.00	2.90	5.50	1.81	10.00	6.83	2.55	1.94	4.20	5.91	3.76
Alginic Acid®H/FD Lot 610321	Alginic acid ISP/USA	5.87	7.60	3.24	4.56	2.88	5.68	0.00	0.00	2.19	3.33	2.28	10.00	6.73	3.56	1.89	2.76	6.14	3.78
Kelacid®Lot 05-GU-235	Alginic acid ISP/USA	5.83	7.89	3.74	5.23	1.40	5.49	0.00	0.00	1.60	10.00	2.23	5.70	6.86	3.46	1.83	5.80	3.97	3.90

The objective of this study was to analyze the index of good compression (IGG) for 43 disintegrants, in order to obtain their profiles and to verify their application in a formulation, with the percentage of excipient that enables an ODT to be obtained by direct compression with no lyophilization. To evaluate the ideal compressibility characteristics of a disintegrant excipient, a SeDeM Diagram expert system was used.

The SeDeM Diagram expert system [6–8] is a new method that has already been used in tablet preformulation studies. It is based on the concept of Quality by Design described in ICH Q8 [9], since it evaluates critical quality attributes that have an impact on the final product's quality. The SeDeM Diagram expert system provides the profile of excipients and active product ingredients (API) in powder form, with respect to their suitability for direct compression. This profile indicates whether a powder can successfully be compressed by direct compression technology or whether it needs to be adjusted with appropriate additional excipients. In addition, this SeDeM Diagram expert system could be seen as an innovative Quality by Design (ICH Q8) tool, since it evaluates factors that are not studied in the traditional drug formulation method and provides information about which properties can be improved. Thus, this tool helps the formulator to design robust processes which can influence the quality of the final product when it is marketed.

2. Materials and methods

2.1. Material

Forty-three excipients were studied, of which 42 had disintegrant properties. The remaining excipient, Copovidone (Plasdone®5630), is an agglutinant and binder rather than a disintegrant. However, it was selected because the molecule is chemically very similar to crospovidone.

The excipients were classified according to their chemical composition into eight families: 19 microcelluloses, 1 multifunctional excipient (with improved disintegrant properties), 3 alginic acids, 4 maize starches, 2 sodium starch glycolates, 7 carboxymethylcelluloses, 5 povidones, and 2 silicate derivates. All are listed in Table 1.

2.2. Methods

2.2.1. Determination of the index of good compression

As established in early papers [6–8], the IGC was determined by the new SeDeM Diagram method, which is based on the experimental study and quantitative determination of the characterization parameters of powdered substances. These parameters are as follows:

- Bulk density (Da): according to Ph Eur 2.9.15 [10].
- Tapped density (Dc): according to Ph Eur 2.9.15 [10].
- Inter-particle porosity (Ie).
- Carr index (IC): according to Ph Eur 2.9.15 [10].
- Cohesion index (Icd): with a Bonals® (Cornellà del Llobregat – Spain) continuous eccentric tablet press [6–8].
- Hausner ratio (IH): according to Ph Eur 2.9.15 [10].
- Angle of repose (α): according to USP, Ph Eur, and RFE [11–13].
- Powder flow (t''): according to USP and RFE [11–13].
- Loss on drying (% HR): according to Ph Eur 2.2.32 [14].
- Hygroscopicity (% H): determination of the sample weight increase after being kept in a humidifier at an ambient relative humidity of 76 ± 2% and a temperature of 22 ± 2 °C until getting constant weight.
- Particle size (% Pf): according to Ph Eur 2.9.12, using a CISA vibrator and sieves of 50 μm [15].
- Homogeneity index ($I\theta$): according to Ph Eur 2.9.12, using a CISA vibrator and sieves of 50 μm, 100 μm, 212 μm, and 355 μm [15].

The parameters were obtained in accordance with the described methodology (SeDeM Diagram) and were converted to diagram radius by applying the equations proposed by Suñé-Negre et al. [6–8].

The SeDeM Diagram expert system has 12 parameters which Suñé-Negre et al. classified into five factors [6–8]. This classifica-

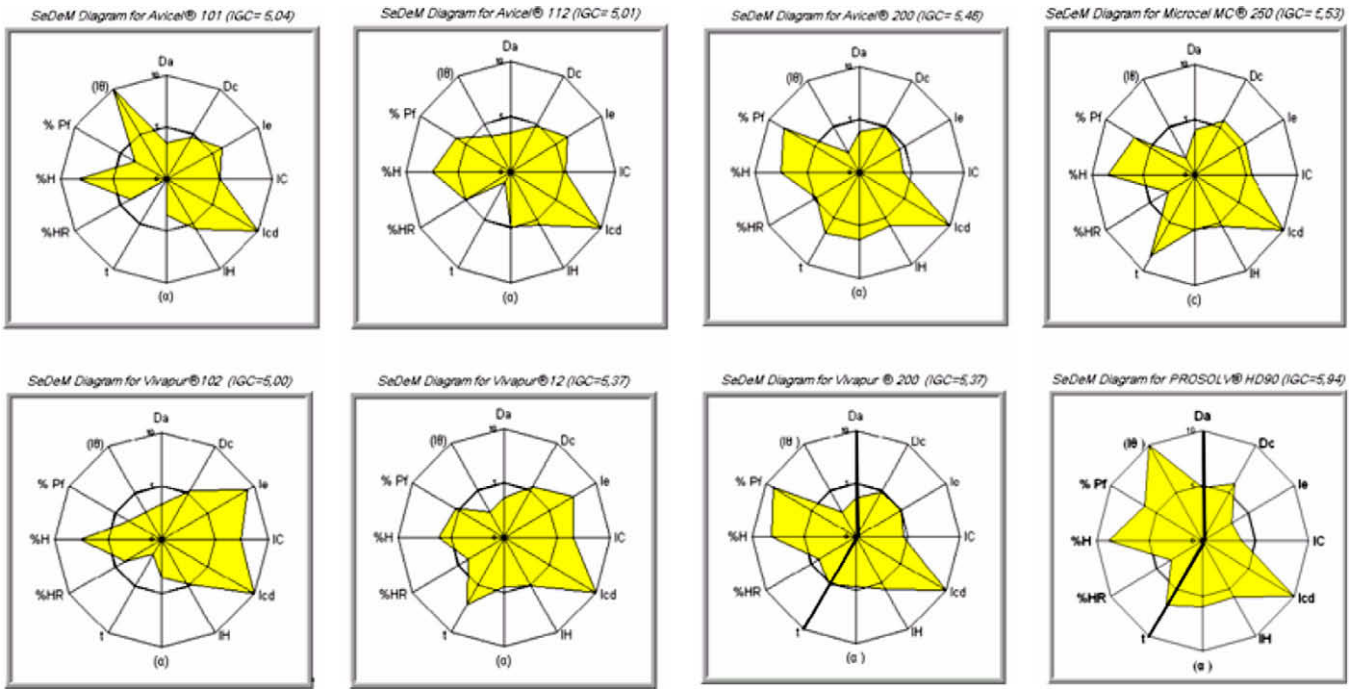


Fig. 1. SeDeM Diagram for microcrystalline celluloses analyzed.

tion was carried out to clarify which factors needed to be improved by the addition of another excipient or API in the final formulation. These five factors are as follows:

- Dimensions.
- Compressibility.
- Flowability/powder flow.
- Lubricity/stability.
- Lubricity/dosage.

Therefore, if a direct compression formulation of tablets (for example, an ODT such as a mouth-dissolving tablet) with a high percentage of these disintegrants is required, an appropriate API or other excipients with good rheological characteristics must be used. This excipient or API must increase the ability to compress the final formula. In other words, it must cover any of the disintegrant's parameters that are below 5. Thus, a final formulation (combination of API + disintegrant) is obtained with a good IGC (5 and above). According to the SeDeM Diagram [6–8], when the final formulation has an IGC of at least 5 the, formula is appropriate for obtaining tablets by direct compression.

3. Results

3.1. IGC evaluation

The results for the disintegrants under study, according to the SeDeM Diagram expert system, are shown in Table 1, which shows that 9 disintegrants were found with an IGC value equal to or higher than 5.

The results show that most of the excipients with an IGC value above 5 were microcrystalline celluloses, except for Pharmaburst®C1, which is a multifunctional excipient whose disintegrant and compressibility properties have been improved by the producer. The other families of disintegrants had an IGC below 5. In fact, these results are logical, as disintegrant excipients are normally used in a low percentage in a tablet formulation. It is well known that these chemical substances have poor properties when used as diluents with no other excipients in direct compression.

4. Discussion

4.1. Analysis of the disintegrant with the best IGC

Table 1 and Fig. 1 show that Avicel®101 (IGC = 5.04), Avicel®112 (IGC = 5.01), Avicel®200 (IGC = 5.46), Microcel®MC 250 (IGC = 5.53), Vivapur®102 (IGC = 5.00), Vivapur®12 (IGC = 5.37), Vivapur®200 (IGC = 5.37), and Prosolv®HD90 (IGC = 5.05) all had IGCs equal to or higher than 5. Table 1 shows that these excipients have good compressibility properties. This is to be expected as the compound is microcrystalline cellulose, which is usually used in a high percentage in tablet formulations. With respect to lubricity/stability, all of these excipients had similar high values (of around 6) as they have some lubricant properties that make them useful in tablet formulation [16].

Pharmabust®C1 is a multifunctional excipient with IGC = 5.52. The high ICG was expected as this excipient has been improved by the supplier to be used as a quick dissolve delivery system in tablets. Table 1 and Fig. 2 show that the following Pharmabust®C1 factors had high values: dimension (5.06), compressibility (5.89), flowability/powder flow (6.53), and lubricity/stability (6.21). However, the lubricity/dosage (4.93) factor needs to be increased. It seems that this factor could easily be improved by adding the mixture of lubricant proposed by Suñé-Negre et al. in an early article [8].

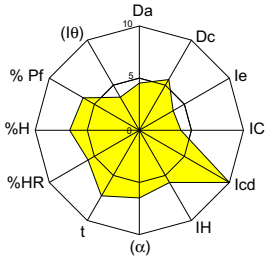


Fig. 2. SeDeM Diagram for Pharmabust®C1.

Examining other disintegrant families in Table 1 and Figs. 3–7, it can be noted that there is a representative of each chemical family [Aquasorb®A500 (IGC = 4.60), Brenncel-DIS® (IGC = 4.90), Nymcel®ZSD-16 (IGC = 4.60), Poliplasdone®XL-10 (IGC = 4.82), and Rxcipients®FM 1000 (IGC = 4.47)] with a value of IGC that is close to 5. Therefore, the obtained parameters can be analyzed and improved with an ideal API and/or additives.

For example, Table 1 and Fig. 4 demonstrate that Brenncel-DIS® (compressibility factor = 1.94) requires improvement in the compressibility factor. This is because particles in this excipient have a regular form (spherical). Therefore, elastic recovery properties are a constraint in the final formulation, as when these types of particles are compacted (plasticity), they try to recover their original form [18]. In addition, the size of particles in Brenncel-DIS® is significantly higher than 200 μm. This could affect the compressibility factor, due to the very low inter-particle forces [18].

Fig. 6 and Table 1 show that Poliplasdone®XL-10 has good values for compressibility (6.97) and flowability/powder flow (5.16). However, lubricity/stability (2.65) and dimension (4.53) factors need to be improved, as the values are below 5. These results were expected, as particles in this excipient are very small. After a review of the information, it was found that the supplier recommends adding a product with a higher density to facilitate the use of this excipient in direct compression. However, lubricity/stability is also expected to be improved, as Polyplasdone®XL-10 is hygroscopic [17].

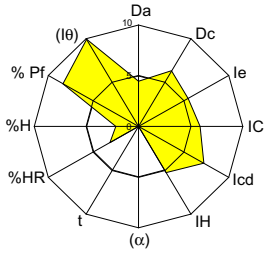


Fig. 3. SeDeM Diagram for Aquasorb®A500.

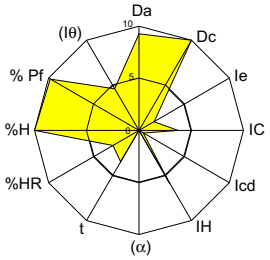


Fig. 4. SeDeM Diagram for Brencel-Dis®.

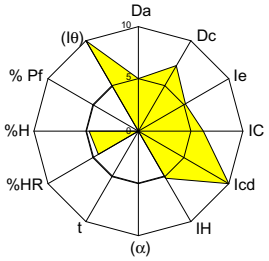


Fig. 5. SeDeM Diagram for Nymcel®ZSD-16.

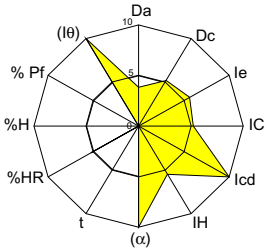


Fig. 6. SeDeM Diagram for Poliplasdone®XL-10.

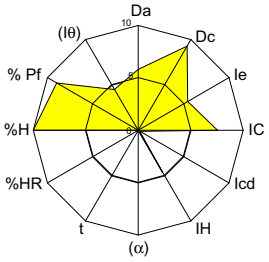


Fig. 7. SeDeM Diagram for Rxcipient®FM1000.

The flowability/powder flow factor needs to be improved in Aquasorb®A500 (1.76), Brenncel-DIS® (3.12), Nymcel®ZSD-16 (1.72), and Rxcipients®FM 1000 (1.55) but not in Poliplasdone®XL-10 (5.16), as shown in Table 1. This is due to the fact that their angles of repose and flowability are not optimal according to the requirements of the SeDeM methodology [19–22].

The lubricity/dosage factor does not need to be improved in Brenncel-DIS® (IGC = 7.20), Aquasorb®A500 (IGC = 9.16), Poliplasdone®XL-10 (IGC = 5.00), Rxcipients®FM 1000 (IGC = 6.73), and Nymcel®ZSD-16 (IGC = 5.00).

4.2. Analysis of the disintegrant by chemical family

An evaluation was carried out that took into account the chemical families of the disintegrants. The chemical families analyzed are as follows:

- Microcrystalline cellulose: cellulose [CAS Number: 9004-34-6].
- Starch derivates: consist of amylose and amylopectin, two polysaccharides based on α-glucose [CAS Number: 9005-25-8].
- Sodium starch glycolate [CAS Number: 9063-38-1] sodium salt of a carboxymethyl ether of starch, containing 2.8–4.2% sodium.
- Sodium carboxymethylcellulose [CAS Number: 9004-32-4], the sodium salt of a polycarboxymethyl ether of cellulose.
- Alginic acid [CAS number: 9005-32-7] is a linear glycuronan polymer consisting of a mixture of β-(1 → 4)-D-mannosyluronic acid and α-(1 → 4)-L-gulosyluronic acid residues, of general formula $(C_6H_8O)n$.
- Crospovidone is a 1-ethenyl-2-pyrrolidinone homopolymer [CAS Number: 9003-39-8].
- Copovidone is acetic acid ethenyl ester, a polymer with 1-ethenyl-2-pyrrolidinone [CAS Number: 25086-89-9].

And the following inorganic compounds:

- Magnesium aluminium silicate, type IB [CAS Number: 1327-43-1].
- Calcium silicate [CAS Number: 1344-95-2].

A bibliographic summary of these excipients, classified by chemical family, is provided in Table 2, so that the main characteristics and mechanism of the disintegrants can be analyzed. This table shows that the percentage of disintegrant required in the formulation of tablets is lower (0.5–15%) than the quantity advised by the expert system. In addition, most of the crospovidone and starch derivates are hygroscopic. Therefore, if a higher percentage of these excipients is used to manufacture a tablet, the tablet will be requiring special packaging to avoid humidity-related problems.

With respect to the experimental results (Table 1), the *microcrystalline cellulose derivates* had good compressibility properties. These excipients are commonly used in a high percentage as their role is primarily to that of a binder/diluent in oral tablets. The dimension factor was under 5, as microcrystalline cellulose is known to be a powder composed of porous particles. This can be noted in the analysis of bulk and tapped density. All of the lubricity/stability values were high and similar, as these excipients have some inherent lubricant properties that make them useful in tableting. In addition, it can be verified that hygroscopicity values were above 5 in all cases. This contributes to make the lubricity/stability factor ideal in all of these excipients. Thus, the lubricity/stability score for this compound was low [16]. The lubricity/dosage factor was not uniform in the microcrystalline cellulose derivates, since the excipients analyzed (Avicel®, Vivapur®, Emconcel®, Microcel®, etc.) have different particle size, as can be noted by analyzing the homogeneity index ($I\theta$) and the particle size (% PF).

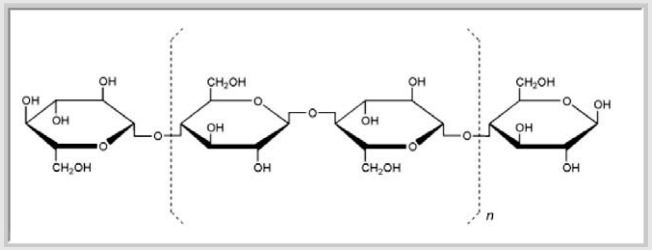
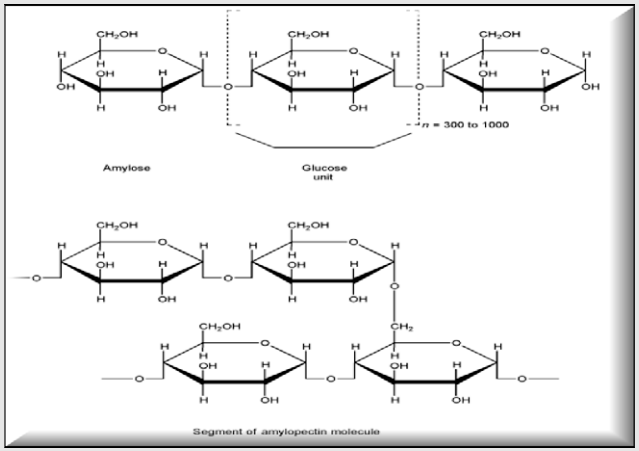
The *derivates of sodium carboxymethylcellulose* were analyzed. IGC values above 4 but lower than 5 were found, except in Cekol®30,000A (IGC = 2.66), as shown in Table 1. The SeDeM method can evaluate differences between excipients that have the same chemical composition but come from the different suppliers or raw material manufacturers.

With respect to the lubricity/dosage factor, Cekol®30,000A had a value of 1.23, the lowest value of all the sodium carboxymethylcellulose derivates. A review of a previous analysis of particle size by laser (Beckman coulter LS Particle Size Analyser) for sodium carboxymethylcellulose derivates, as detailed in Table 3, shows that Cekol®30,000A has a greater percentage of particles bigger than 200 μm than the other sodium carboxymethylcellulose derivatives. These results confirm that excipients with particle sizes above 200 μm are not easily compressed [19,23].

The lubricity/stability factor was very low for all the sodium carboxymethylcellulose derivates. This may be due to the fact that this group of excipients is hygroscopic and absorbs significant amounts of water at temperatures up to 37 °C and relative humidities of about 80%, as can be seen in Table 2 [19,23,24].

Flowability/powder flow factors were expected to have high levels in all sodium carboxymethylcellulose derivates, as these excipients are used in a high percentage and are one of the main ingredients of self-adhesive ostomy. Therefore, a high percentage

Table 2
Characteristics of the chemical family of the excipients analyzed.

Chemical family	Structure	% Commonly used	Solubility	Humidity	Mechanism of disintegration
Microcrystalline cellulose		5%–15%	Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents	Typically less than 5% w/w	Swelling
Alginic acid	Mixture of β-(1 → 4)-D-mannosyluronic acid and α-(1 → 4)-L-gulosyluronic acid residues	1%–5%	Soluble in alkali hydroxides, producing viscous solutions; very slightly soluble or practically insoluble in ethanol (95%) and other organic solvents	7.01%	Swelling
Starch		3%–15%	Practically insoluble in cold ethanol (95%) and in cold water	Commercially available grades of corn starch usually contain 10–14% water	Swelling Deformation

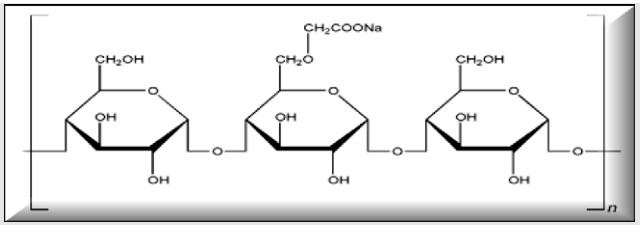
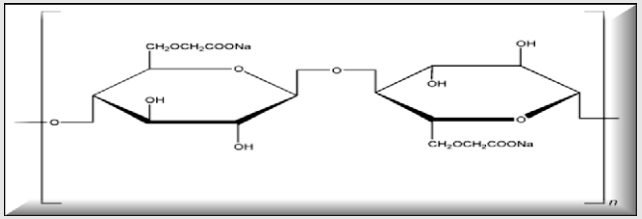
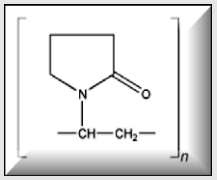
Sodium starch glycolate		2%–8%	Sparingly soluble in ethanol (95%); Practically insoluble in water. At a concentration of 2% w/v sodium starch glycolate disperses in cold water	Not more than 10.0%	Rapid and extensive swelling with minimal gelling
Sodium carboxymethylcellulose		0.5%–5%	Practically insoluble in acetone, ethanol (95%), ether, and toluene. Easily dispersed in water at all temperatures. Forming clear, colloidal solutions	Typically contains less than 10% water	Wicking due to fibrous structure, swelling with minimal gelling
Crospovidone		2%–5%	Practically insoluble in water and most common organic solvents	Maximum moisture sorption is approximately 60%	Water wicking, swelling and possibly some deformation recovery
Calcium silicate	Inorganic compound	*	Practically insoluble in alcohols, water and organic solvents	1%	*Swelling but it is used as synergic with other excipient
Magnesium aluminium silicate	Inorganic compound	*	Practically insoluble in alcohols, water, and organic solvents	6.0%–9.98%	*Swelling but it is used as synergic with other excipient

Table 3
Test results of particle size analysis of sodium carboxymethylcellulose derivates.

Product	Particle size analysis (μm)			
	Average	D10	D50	D90
Aquasorb®A500	61.51	13.31	49.22	127.6
Nymcel®ZSB16	63.39	14.52	45.41	142.9
Nymcel®ZSD-16	36.57	5.203	32.64	70.61
Nymcel®ZSX-W	20.03	2.163	18.06	41.32
Nymcel®ZSB-10	46.44	12.69	38.72	94.24
Cekol®30,000 A	118.1	24.46	99.45	243.1
Nymcel®ZSX	46.99	5.216	36.25	100.4

D10 means that 10 vol.% of the flake substrate particles has a size up to that value.
D50 means that 50 vol.% of the flake substrate particles has a size up to that value.
D90 means that 90 vol.% of the flake substrate particles has a size up to that value.

of this excipient is expected to increase the adhesive properties between particles [19].

Table 1 reveals that all *starch derivates* had IGC values below 5. Lycatab®C (IGC = 4.04) and Starch®1500 (IGC = 4.78) (which are partially pregelatinized starches) had the highest values, probably because pregelatinized starch has been chemically and/or mechanically processed to rupture all or part of the starch granules, and thus, render the starch flowable and directly compressible [21]. However, the compressibility factor was around 4. Therefore, according to the SeDeM expert system, this factor still needs to be improved.

The dimension factor was at an ideal level in all starches derivates. The compressibility results were expected, as a previous paper on these excipients indicated that they do not compress well and tend to increase tablet friability and capping if they are used in high concentrations [21].

The flowability and powder flow factor need to be improved in this group. This result was also expected, as the literature indicates that starch derivates have cohesive properties and poor flow characteristics.

The lubricity/stability factor needed to be improved, as starch derivates are hygroscopic and rapidly absorb atmospheric moisture [21,25,26]. At an approximate equilibrium of 50% relative humidity, the moisture content values were 11% for corn starch. Between 30% and 80% relative humidities, corn starch was the least hygroscopic, starch and potato starch was the most hygroscopic. Commercially available grades of corn starch contain between 10% and 14% water.

IGC levels below 5 were found in all *crospovidone and copovidone derivates*. The dimension factor needs to be improved in these derivates. However, the compressibility factor does not need to be improved in any case, as all of the values obtained were higher than 5. The flowability/powder flow factor needs to be improved in all crospovidone and copovidone derivates, except for Poliplasdone®XL-10. The lubricity/stability factor needs to be improved in all crospovidone and copovidone derivates. Crospovidone had a maximum moisture sorption of approximately 60%, and copovidone derivates had a higher value of this factor, as at 50% relative humidity, copovidone gained less than 10% weight [17,27,28].

The lubricity/dosage factor needs to be improved in Kollidon®CL and Poliplasdone®XL. According to information received from the supplier, the size of particles in Plasdone®S630 is higher than 200 μm. The size of particles in Poliplasdone®XL-10 is lower than 100 μm. These characteristics seem to lead to an improvement in the IGC.

Table 1 shows the *inorganic compounds* that were analyzed (calcium silicate and magnesium aluminium silicate). Both of these had IGC values under 5. The compressibility and flowability/powder flow factors need to be improved in both of these compounds. This result was expected, as when the analysis was performed, it was noted that the appearance and texture of these compounds were similar to talc and the particles were smaller than the other products analyzed. These characteristics do not help flowability properties, as they lead to higher inter-particle and Van der Waals forces. The compressibility factor needs to be improved, as during the experimental assay a high percentage of tablets containing these excipients were found to be capped [22].

Table 1 shows an analysis of *sodium starch glycolate* derivates. These excipients have IGC values above 4 but below 5. The compressibility factor generally needs to be improved in these compounds, as particles in these derivates have a regular form (spherical) [18]. Consequently, elastic recovery properties are a constraint in the final formulation, as when these types of particles are compacted they try to recover their original form. An analysis of Table 1 reveals that there is a difference in the compressibility of Glycolys® and Brenncel-DIS®. This is due to the moisture content of these excipients, which affects their compatibility and compressibility, according to Young et al. [29].

The analysis of *alginic acid derivates* in Table 1 revealed values below 5. The factors that need to be improved in alginic acid derivates are compressibility and flowability/powder flow. This result was expected, as the appearance and texture of these compounds are similar to talc. In addition, the particles were smaller than the other products analyzed, which does not help flowability as it leads to higher inter-particle and Van der Waals forces [20,30,31].

The compressibility factor also was expected to be improved after the experimental assay, as it was found that lower values of hardness were obtained with these products.

Finally, Table 4 summarises the SeDeM experimental characteristics of each chemical family of disintegrants analyzed to facilitate the formulation of disintegrants by direct compression. We proposed determining the SeDeM of the API, with respect to the 5 parameters used in the method (dimension, compressibility, flowability/powder flow, lubricity/stability, and lubricity/dosage).

Table 4
Analysis by chemical family of the value obtained for the 5 SeDeM factors.

Chemical family	Dimension	Compressibility	Flowability/powder flow	Lubricity/stability	Lubricity/dosage
Microcrystalline cellulose	+++++	+++++++	+++	++++++	+++++
Alginic acid	+++++	+++	++	++++	+++++
Starch	+++++++	++++	+++	+++++	++++
Sodium starch glycolate	++++++++++	+	++++	++++	++++++
Sodium carboxymethylcellulose	++++++	++++++	++	+++	++++++[a]
Crospovidone/copovidone	++++[b]	++++++	++++	+++	+++++[c]
Calcium silicate/magnesium aluminium silicate	++++++	+++	++	+++++	+++++++

+ = bad.
++++++++ = very good.
[a] Cekol 30,000A +.
[b] Kollidon VA 64 fine ++.
[c] Kollidon VA64 fine ++++++++++.

If, for example, the dimension of the API needs to be improved, sodium starch glycolate could be the first choice of additive, as this family has the best characteristics for forming tablets with no dimension problems. In contrast, if the compressibility of the API needs to be improved, microcrystalline cellulose should be added. If improvements need to be made to the flowability/powder flow, sodium starch glycolate and crospovidone could be used. If the problem is related to lubricity/stability, the formulation could be improved with microcrystalline cellulose. Finally, lubricity/dosage could be improved with calcium silicate or magnesium aluminium silicate. Additional lubricant must be added to the formula to improve the flow of the formulation.

5. Conclusions

As documented previously, the SeDeM Diagram is a useful and effective tool for accurately evaluating the characteristics and physical properties of excipients. The method provides sufficiently reliable and reproducible results for the characterization of substances (APIs or excipients) with respect to their suitability for direct compression [6–8]. In this case, the method was applied to diluents and disintegrants for pharmaceutical use. The analysis showed that 9 excipients had IGC higher than 5, and can therefore be compressed directly to produce orally disintegrating tablets. With respect to the disintegrants and their chemical families (except for the family of microcrystalline cellulose), the disintegrants did not have good characteristics for use in direct compression as the only excipient in the formula, as IGC values were lower than 5. However, some disintegrants like Brenncel-Dis®, Aquasorb®A500, Poliplasdone®XL-10, Rxcipients®FM 1000, and Nymcel®ZSD-16 had IGC values near to 5, which indicates that they could be used in direct compression if an appropriate API (with suitable SeDeM properties) or a few other excipients were added to obtain a final formulation (combination of API + excipient) with an IGC higher than 5. The SeDeM Diagram expert system can be used select a suitable active pharmaceutical ingredient (API) or excipient.

The results obtained (IGC value below 5) were logical, as it is well known that disintegrants do not have either good lubricity or flowability. Generally, these excipients are used in smaller quantities that do not affect the other components of the final formulation in terms of lubricity, flowability, or compressibility.

Finally, an analysis of chemical families was performed. It was found that the microcrystalline cellulose family had the best IGC values. This result was expected, as these excipients are commonly used in higher percentages since their role is primarily as binders/diluents with good compressibility properties. In terms of the other chemical families, sodium starch glycolate derivates had good IGCs of nearly 5. The levels will be verified in future research, as these derivates are known to be superdisintegrants, which can help to obtain oral disintegration tablets by direct compression technology. In this future study, we will analyze the effect of a high percentage of these excipients on disintegration time.

Finally, we conclude that the SeDeM Diagram expert system could be used to differentiate between excipients and their chemical families or to evaluate the same excipient from different suppliers.

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