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REVIEW

SeDeM Expert System: A review and new perspectives

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Abstract: The SeDeM Expert System was first known as a galenic pre-formulation system, which was based on the experimental research and quantitative determination of powdered substances. And the mathematical formula provided by the SeDeM Expert System has plays an important role in the study of powder properties. The system can be used not only to evaluate the powder direct compression (DC) of excipients and active pharmaceutical ingredients (API's), but also to predict the possible formulations, so it can reduce unnecessary research and trials, and shorten the time of development. In this paper, the research development and application of SeDeM Expert System in DC was summarized, and the results showed that with a few exceptions, the system was skilled in predicting acceptable tablet formulations. Finally, the new application prospect of the system is presented, including the application of the Internet traffic and content management (iTCM) database and the new co-processed excipients.

Keywords: SeDeM Expert System, radar graph, powder, direct compression, pre-formulation, co-processed

1 Introduction

Because of its simple process, convenience for the patient, accurate dose administration, and better stability than other dosage forms, tablet has become the most prevalent oral dosage forms in clinics. The primary manufacturing techniques of tablet are dry-granulation, wet-granulation and direct compression (DC) of dry powders. Over the past few decades, wet-granulation was widely used in pharmaceutical industry because of that the products of wet granulation have many advantages, such as beautiful appearance, good fluidity, strong wear resistance and good compression formability, even though it takes a long time and have high cost. Due to the emergence of various new excipients, the production of tablets is now changing to DC and high-speed production,[1] and compared with traditional wet-granulation process, DC can effectively avoid the granulation process, reduce the order of production, shorten the period of production and increase the rate of bioavailability.

There is no doubt that in the solid tablet manufacturing, DC is the best ones. However, DC is not applicable to all of the material tableting. Since DC is a process that does not pass through the granulation and the powder is directly mixed, it is possible to have a material that is not suitable for tableting, or the mixing is not uniform, which will seriously hinder the process of DC,[2] and what's more, it will make it difficult for the tablets to be produced. All of these are the basic reasons why DC is not widely used. In order for DC to be used more widely, the SeDeM Expert System was proposed in 2005 by Suñé Negre, *et al*.[3]

SeDeM Expert System known as "Sediment delivery model", it's an innovative tool developed by the University of Barcelona to characterize the powder, and it has been widely used in many preparation experiments and has proved to be powerful. The final result of the system is presented by SeDeM diagram. The dimension, compressibility, flow ability/powder flow, lubricity/stability, lubricity/dosage dose and so on, provided by SeDeM diagram, can be used to characterize the physical properties of the powder, including pressure, and the like.[4] According to the SeDeM diagram, it can intuitively indicate whether a substance is suitable for DC, and through the formula provided by SeDeM Expert System, it can get the minimum number of excipients needed for API's. SeDeM Expert System can be combined with prescription design effectively, which is of practical significance

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to reduce the cost of drug development and improve the final quality of the product.

As the summary of SeDeM Expert System in 2005 to 2019, most of them have reviewed the principle of SeDeM Diagram and SeDeM-ODT, but few have reviewed the research progress and application of SeDeM or SeDeM-ODT Expert System. In this paper, the research mainly development of SeDeM Expert System and its application in DC was summarized, and the new application prospect of SeDeM Expert System was presented, including the application of new co-processed excipients.

2 Development of SeDeM Expert System

The SeDeM Expert System was first proposed in 2005,[3] and it is mainly used to characterize the properties of powders to help pre-preparation determine the appropriate production process and whether it is suitable for direct pressing.[5] From the relevant literature, we can see that before 2012, SeDeM Expert System did not get much attention. However, with the maturation of DC technology, SeDeM Expert System has been widely used since 2012. With the development of SeDeM Expert System, it plays a more and more important role in the study of different powder properties and the design of direct tablet formulation. At the same time, improving and increasing the indicators of the system, make the results be more accurate and applicable.

2.1 Initial SeDeM Expert System

2.1.1 The main parameters

The initial SeDeM Expert System is mainly used to evaluate the direct compression properties of powders, and its main parameters are mostly related to the properties of powders. The system is consists of 5 primary indexes, and they are considered as the following:

- Dimension
- Compressibility
- Flow ability/Powder flow
- Lubricity/Stability
- Lubricity/Dosage

At the same time, the above 5 primary indexes are composed of 12 second-level indicators. Referring to the study of the European Pharmacopoeia and the research of Suñé Negre, *et al.*, the 12 second-level indicators were studied, and the results of these powder tests were treated with the equation shown in Table 1.[3] The results in Table 1 are standardized in accordance with the calculation method in Table 2, and the resulting data are used to draw the radar map (SeDeM Diagram), as shown in Figure 1. The SeDeM Diagram intuitively shows the 12 second-level indicators of the powder, and combines the calculation formula to determine whether the powder is suitable for DC. The 12 second-level indicators are considered as the following:

- Bulk density (Da)
- Tapped density (Dc)
- Carr index (IC)
- Inter-particle porosity (Ie)
- Cohesion index (Icd)
- Angle of repose (α)
- Hausner ratio (IH)
- Powder flow (t")
- Loss on drying (% HR)
- Hygroscopicity (%H)
- Homogeneity index (Iθ)
- Particle size (%Pf)

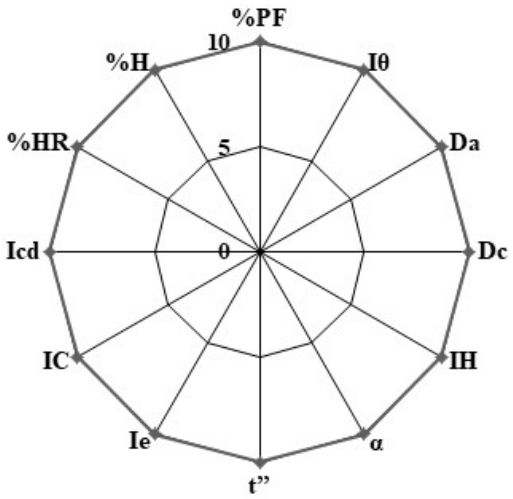

Figure 1. SeDeM Diagram

2.1.2 Powder compressibility evaluation

Based on the radius values of 12 second-level indicators of powder physical fingerprint spectrum in SeDeM Expert System, the parameter index (index of parameter, IP), parameter contour index (index of parametric profile, IPP) and the good compressibility index (the index of good compressibility, IGC), can be constructed respectively. It is used to judge the compressibility of powder and to speculate whether it is suitable for direct pressing of powder. The number of physical exponents defined as radius $\geq$ 5 is a percentage of the total number of physical indexes in the physical fingerprint spectrum, and the acceptable range is IP $\geq$ 0.5. The parameter contour index is defined as the average of the radius values of all physical indexes, and the acceptable range is IPP $\geq$ 5.The calculation method of good compressibility index: IGC = IPP $\times f$, and the acceptable range is IGC $\geq$ 5. For 12 second-level indicators f value =

Table 1. Parameter and equation used by SeDeM Expert System

Incidence factor	Parameter	Symbol	Unit	Equation
Lubricity / Dosage	Particles < 50 μm	%P*f*	%	Experimental
	Homogeneity index	Iθ	-	Iθ=Fm/100+ΔFmn
Dimension	Compressibility	Da	g/mL	Da=P/Va
	Tapped Density	Dc	g/mL	Dc=P/Vc
	Hausner Ratio	IH	-	IH=Dc/Da
Flowability / Powder flow	Angle of Repose	α	°	$\tan\alpha = h/r$
	Powder Flow	t"	s	Experimental
Compressibility	Interparticle porosity	Ie	-	Ie = Dc –Da/Dc*Da
	Carr Index	IC	%	IC = (Dc –Da/Dc)100
	Cohesion Index	Icd	N	Experimental
Lubricity/Stability	Loss on Drying	%HR	%	Experimental
	Hygroscopicity	%H	%	Experimental

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

Incidence factor	Parameter	Unit	Limit value (v)	Factor applied to v
Lubricity/Dosage	% P*f*	%	50~0	10−(v/5)
	Iθ	-	0~0.02	500v
Dimension	Da	g·mL-1	0~1	10v
	Dc	g·mL-1	0~1	10v
Flowability/Powder flow	IH	-	3~1	(30−10v)/2
	α	°	50~0	10−(v/5)
	t"	s	20~0	10−(v/2)
Compressibility	Ie	-	0~1.2	10v/1.2
	IC	%	0~50	v/5
	Icd	N	0~200	v/20
Lubricity/Stability	%HR	%	10~0	10−v
	%H	%	20~0	10−(v/2)

0.952.

The more the number of physical indexes in the physical fingerprint spectrum is, the larger the polygon area is, and the greater the reliability factor f is.

2.1.3 Powder compressibility correction

When the compactness of powder is poor (IGC<5), the 5 primary indexes (piling, homogeneity, fluidity, compressibility and stability) can be corrected by adding appropriate kinds and proportion of excipients. To make it meet the requirements of compressibility. The correction method is to calculate simultaneously the minimum amount of excipients needed to meet the minimum radius value of each index of the API. The formula is as follows:

$$\mathrm{CP} = 100 - \frac{\mathrm{RE} - \mathrm{R}}{\mathrm{RE} - \mathrm{RP}} \times 100 \qquad (1)$$

CP indicates the percentage of adjuvants used for correction, RE denotes the mean radius of physical indexes of auxiliary materials for correction, R represents the expected physical index radius (5 is the minimum expected correction), RP represents the average radius of the physical index of the Chinese herbal extract powder to be corrected.

If the compressibility index of the API powder IGC is less than 5, it is optional to mix it with an excipient with a good quality attribute (first-order index average > 5), According to Equation 1, the amount of correction excipients needed to be added in theory can be obtained by calculation of re and RP which are expected to reach to R=5 and are calculated with radius value.

2.2 Optimization of the parameters

2.2.1 Optimization of IH

It can be seen from the formula in Table 1 that Da = P/Va, Dc = P/Vc, and IH = Dc/Da, so we can prove that IH = Va/Vc (Where Va, initial volume and Vc, final volume). In general, the compacted powder (V_c) is lower than bulk volume (V_a). However, due to some factors such as the interaction between particles affecting the spatial distribution of particles, the V_c value may also be higher than V_a.

By using SeDeM Expert System, 22 kinds of excipients were experimentally studied. Ans the results show that the limit range of IH of these excipients is 1.1 to 2.46. Considering the possibility of appearing outside the range of the interval and making the calculation easier, the interval of IH is adjusted to 1 to 3, and an exception value less than 1 shall be treated as a non-current or almost non-current product with a radius of 0, as shown in Table 3.[6]

Table 3. Parameter and equation used by SeDeM radius

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

2.2.2 Optimization of %HR

%HR is get by doing experiments, and in order to make the standardization conversion more convenient, some researchers characterized 22 kinds of excipients by SeDeM Expert System and simplified them by two methods. The first is to convert it by different calculation methods, and the second is to divide the range of %HR according to the experimental results. By comparison, the second method is better. According to the experimental results, the relative humidity parameters are divided into three regions. Humidity less than 1% indicates that the powder is very dry and easy to produce static electricity to hinder the flow of the powder. Humidity above 3% indicates that the powder is too wet, which easily leads to agglomeration and makes the fluidity worse, and also makes it stick to the punching plate and the template. Therefore, 1% to 3% is the best range for%HR.

2.2.3 Optimization of the Icd

In the established SeDeM Expert System (Table 1), Icd is the only parameter to measure the cohesion of powder.[6]The general method of Icd measurement is to use eccentric press to make 5 elliptical convex pieces of 1 gram (g) with a 19×10 mm punch format with an eccentric press.[7] The average hardness of these 5 tablets is the final value of Icd.[8] From this, we can see that the Icd value is related to hardness.[9] When the final plate weight is fixed at 1 (±0.05) g, the size and thickness of the tablet are the main variables. The main factors affecting these two variables are the physical properties of the powder, such as elastic recovery and bulk density.

Because the physical properties of the powder are different and the bulk density of the different powder is different, there will be a big deviation in the calculation of the Icd with the final slice weight of 1 g. To make the results more accurate, Nofrerias, *et al.*[10] performed SeDeM characterization experiments on several different powders. The Icd is used as the unique variable (the variable experiment of varying the weight of the sheet at different levels is carried out to obtain different Icd values). Compared with the final set of SeDeM Diagrams, they proposed a new Icd determination method. According to different volume densities, different tablet weights are required, for example, high density excipients require

the production of heavier tablets. Otherwise, the production of lighter tablets is required.

2.3 SeDeM-ODT with a new factor: Disgregability

Because of the widespread use of tablets, in order to make the study of pre-formulation more convenient and rapid, the SeDeM Expert System has been further developed. In 2012, Aguilar-Díaz, *et al.*[11] aimed at ODT drugs based on five factors of the SeDeM system. A new factor is added and the concept of SeDeM-ODT is proposed for the first time.

The SeDeM-ODT methodology is composed of 6 primary indexes, which come from 15 second-level indicators. Based on the SeDeM method, it adds an incidence factor index and 2 tests or parameters. The new primary indexe is Disgregability, and it is affected by Effervescence (DE), Disintegration Time with disc (DCD) and Disintegration Time without disc (DSD). The newly added indicators and calculation formulas are shown in Table 4, and the newly added acceptable range of physical quality indicators and standardized conversion methods are shown in Table 5. And the radar image of powder characterization is shown in Figure 2. And in the end, the calculation method of Powder compressibility evaluation and Powder compressibility correction is the same as that of SeDeM.

Table 4. SeDeM-ODT characterizing powder index and calculating formula

Incidence factor	Parameter	Symbol	Unit	Equation
Disgregability	Effervescence	DE	minutes	Experimental
	Disintegration Time with disc	DCD	minutes	Experimental
	Disintegration Time without disc	DSD	minutes	Experimental

Table 5. Acceptable range of physical quality indicators and standardized conversion

Incidence factor	Parameter	Unit	Limit value (v)	Factor applied to v
Disgregability	DE	minutes	0~5	10v
	DCD	minutes	0~3	10v
	DSD	minutes	0~3	10v

2.4 Specific surface area and true density

The SeDeM Expert System depends on the powder properties of the materials, and the results of the materials with different powder properties are different. In order to make the SeDeM results more accurate, some experts proposed a new parameter value.[12] In addition to the 12 secondary indicators that have been proposed, Zhang, *et al.*[13] have proposed two properties: specific surface area and true density. The specific surface area and true density are one of the basic properties of the powder, which has an important effect on the experimental results, such as absorbance. With the addition of two new parameters, the SeDeM Diagram forms a 14-sided polygon, and its accepted reliability (reliability factor = 0.967) is also improved (shown in Figure 3).

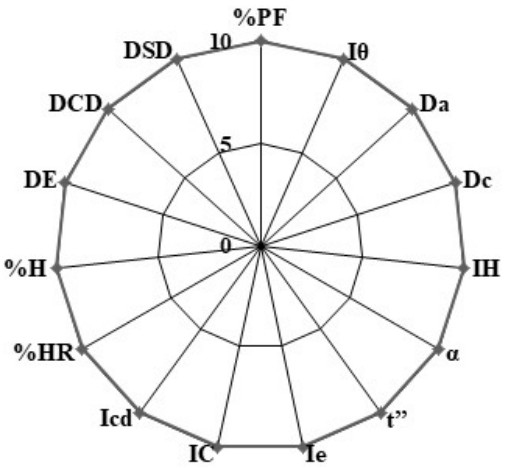

Figure 2. SeDeM ODT Diagram

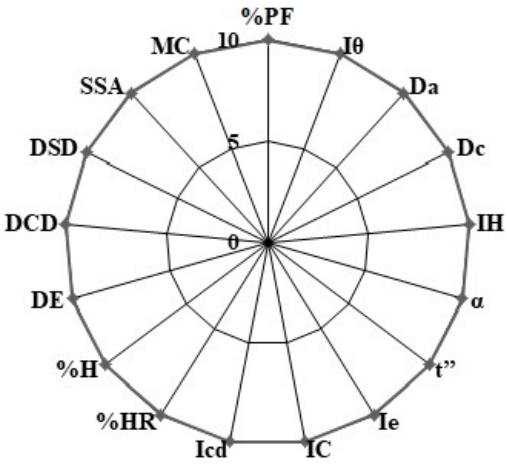

Figure 3. New SeDeM ODT Diagram

3 The application of Expert System

At present, the SeDeM Expert System is mainly used in the research of the DC performance of APIs and excipients, Pre-formulation study and proportion of APIs and auxiliary materials in prescription.

3.1 Evaluation of the suitability of a material for DC

In the study of preparation, the powder properties of APIs and excipients are very important. Different manufacturers, different batches, different types, and different chemical groups of APIs or excipients have different powder properties. So, it is necessary to conduct a comprehensive study of their powder properties.

3.1.1 Research on different batches of material

SeDeM Expert System can be used to prove the acceptability of the straight pressure properties of the materials and to characterize the physical properties of the related powders. Three batches of glucosamine salt F0130 (an API material) were characterized by SeDeM Expert System in order to study the consistency of powder properties of different batches of glucosamine salt F0130.[14] The results show that although the API is not suitable for DC, the materials of different batches have good reproducibility, which shows that the reproducibility of different batches of API is good.

3.1.2 Research on different chemical groups of material

Aguilar-Díaz, *et al.* use the new SeDeM Expert System to analyze the suitability of 43 excipients for DC with separation properties from eight chemical families. Characteristics of the chemical family of the excipients and the analyzed Analysis by chemical family of the value obtained for the 5 SeDeM factors are shown in Table 6 and Table 7.[15]

3.1.3 Research on different types of material

The physical properties of different materials are different, and the SeDeM Diagram can show the difference intuitively. The SeDeM Expert System has practical significance in studying the straightness and the improvement of the straightness of different materials. Suñé Negre, *et al.* performed SeDeM Expert System characterization tests on an API (Glucosamine salt API F0357) and 6 diluents (such as Avicel PH 101 and Kleptose), respectively. The results showed that the API had poor straightness.[16] However, when a small quantity (29.09%) of the excipient Plasdone S630 is added, it can be compressed directly. This experiment shows for the first time that SeDeM Expert System can not only prove the straightness of the material, but also correct the API with a certain dose and kind of excipient. Recently Wan et al corrected the DC properties of rhodiola extract with a certain dose and variety of excipients.[17]

Different materials have different properties of DC. In order to know more intuitively the range of direct pressure of all kinds of materials, Su-Negre et al have characterized 51 kinds of DC excipients through the sSeDeM Expert System.[18] The maximum and optimum values of DC diluents, as well as the parameters, functions and mathematical limits of the direct compressibility level are determined, and their properties are sorted out to form the periodic table of classification of excipients (shown in Figure 4[18]).

3.2 Determination of the amount of excipient in formulation development

In many cases, a single drug or excipient can't be pressed directly, so it is necessary to mix the powder with a certain amount of excipient to improve the poor properties of the single drug. Combined with the modified equation provided by SeDeM Expert System, we can calculate the minimum amount of excipient which can make up for the deficiency of API's directness. Negre et al used SeDeM to characterize an API and 5 kinds of excipients (Avicel ph102, avicel 2000 and others), and finally selected the best excipient. However, the modified equations of SeDeM Expert System are not all valid. Schooltz, *et al.*[19] have studied the ability of SeDeM Expert System to predict the combination of API and excipient concentration according to equation 12. However, considering the fragility of tablets, some of the APIs cannot be pressed directly. At present, SeDeM Expert System is mainly tested on binary powder system. The research of multicomponent powder system is still in progress, and the research method of SeDeM Expert System is also under further study.

3.3 Application of SeDeM Expert System in pre-formulation

With the emergence of the first SeDeM Expert System related literature in 2005, the influence of SeDeM Expert System has grown rapidly. Before 2012, the SeDeM system is not particularly mature, so the application literature is less, mostly the research on its related properties. After 2012, the application of SeDeM Expert System has been growing rapidly.

3.3.1 Pre-formulation study of convention Oral tablets

Oral tablet is the most common dosage form, and DC is the most convenient table pressing technology. With the development of SeDeM Expert System and the maturation of DC, Many researchers have studied the preformulation of oral tablets directly pressed by SeDeM Expert System. SeDeM Expert System can avoid unnecessary experimental formulations and shorten the preparation time for the development of oral tablets suitable for DC.

In 2012, inderbir singh and pradeep kumar used the

Table 6. Characteristics of the chemical family of the excipients analysed

Chemical family	%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	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%	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 starch glycolate	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		Practically insoluble in alcohols, water and organic solvents	1%	Swelling but it is used as synergic with other excipient
Magnesium aluminium silicate		Practically insoluble in alcohols, water, and organic solvents	6.0%–9.98%	Swelling but it is used as synergic with other excipient

SeDeM Expert System to study the pre-formulation of cefuroxime axetil and paracetamol.[20] The results show that SeDeM Expert System can directly show the relevant data of the DC performance of axetil and paracetamol. In 2013, Aguilar-Díaz, *et al.* used the SeDeM Expert System to study ibuprofen prescriptions and obtained 8 prescriptions, which proved the reference value of sedem prescription research on ODT.[21] In 2016, Campiez, *et al.*[22] used the SeDeM Expert System to study the DC ability of carbamazepine. The results showed that carbamazepine had proper direct compression ability.

Here are some related studies combined with SeDeM-ODT: In 2017, Dasankoppa, *et al.*[23] used SeDeM-ODT Expert System to characterize excipients and developed rosuvastatin calcium dispersible tablets. And in the same year, SIPOS, *et al.*[24] used SeDeM and SeDeM-ODT Expert System to study ibuprofen ODT tablets in children. And Campiñez, *et al.*[25] used the SeDeM Expert System to test the prescription design of polyurethane, and found that this biodegradable polymer had good fluidity and could be used in direct pressing tablets. Unnecessary excipient screening is reduced.

3.3.2 Pre-formulation study of sustained-release and controlled release preparations

The sustained-release preparation is a kind of preparation which can continuously release the drug for a long period of time. The release of the drug is mainly a first order rate process. Controlled release preparation is a preparation in which a drug can be automatically released at a predetermined rate within a predetermined period of time, so that the blood drug concentration is kept within the effective concentration range for a long time. Drug release is mainly at zero or near zero within a predetermined period of time.

In 2014, Saurí, *et al.*[26] studied the DC formula of captopril skeleton tablets by SeDeM Expert System, and obtained good results. In 2016, Ofori-Kwakye, *et*

Table 7. Analysis by chemical family of the value obtained for the 5 SeDeM factors

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

al.[27] developed and evaluated two kinds of natural gelatine sustained-release matrix tablets, and they used SeDeM Expert System for the two different water-soluble drugs. Results from the study have shown that light grade cashew gum powder can be used for DC of tablets. And in 2018, Tadwee, *et al.* used SeDeM Expert System to develop losartan potassium sustained-release tablets. The results showed that losartan API was not suitable for direct compression.

3.3.3 Pre-formulation study of other style tablets

The SeDeM Expert System is used not only in the pre-prescription research of oral solid preparations and sustained-release or controlled release preparations, but also in other formulations, such as effervescent tablets, and it is found that the SeDeM Expert System is not only suitable for pre-formulation research of western medicine, it is also applicable to the pre-formulation study of traditional Chinese medicine.

In 2014, Khan, *et al.*[28] studied the development of effervescent tablets with SeDeM Expert System, and explained the applicability of SeDeM Expert System to effervescent tablets. In 2015, Khan, *et al.*[29] used SeDeM Expert System to predict the effects of taste masking on the disintegrating behavior, mechanical strength and rheological properties of highly water-soluble drugs. And In the same year, Campiez, *et al.*[30] studied the DC of a new biodegradable polythiourea controlled release matrix polymer using SeDeM Expert System. The results show that the new synthesized polythiourea has sufficient rheological properties. Borges, *et al.*[31] used SeDeM Expert System to characterizing the active substance and polyvinyilpyrrolidone eliminating metastable forms in an oral lyophilizate, and the use of SeDeM Diagram provided valuable data regarding the stability behavior of CTZ in its solid form.

The following is a study of traditional Chinese medicine and pellets: In 2016, Zhang, *et al.*[32] used SeDeM Expert System to characterize the extract powder of traditional Chinese medicine. The results showed that the establishment of physical fingerprint spectrum of extract powder of traditional Chinese medicine was helpful to the application of QbD in the research and production of traditional Chinese medicine preparation. In 2017, Hamman, *et al.* developed pellets of different sizes based on SeDeM Expert System, and the study have shown that the SeDeM EDS was successfully applied to pellets of different sizes ranging from 0.5 mm to 2.5 mm to identify potential inadequacies for compression into MUPS tablets,and the incidence factor that was identified as a potential shortcoming for compression into MUPS tablets of all the pellet sizes was compressibility.[33] And in the second year, Hamman, *et al.* developed pellets containing different active drug components based on SeDeM Expert System, and the results of this study showed that the SeDeM EDS was successfully applied to pellets containing different active pharmaceutical ingredients for prediction of formulations for preparation of MUPS tablets with acceptable properties.[34]

4 New perspectives

With the improvement of SeDeM Expert System, the data of SeDeM expert system is more and more accurate, and the scope of SeDeM expert system is more extensive.

4.1 The internet traffic and content management (iTCM) database

Since the SeDeM Expert System was put forward, Researchers have used it to characterize a variety of APIs and excipients, and a lot of relevant data have been obtained. The related data of powder properties were summarized and the iTCM database was obtained. The iTCM database is the largest and the solely one at present based on the SeDeM Expert System, and it laid the foundation of the knowledge space under the framework of

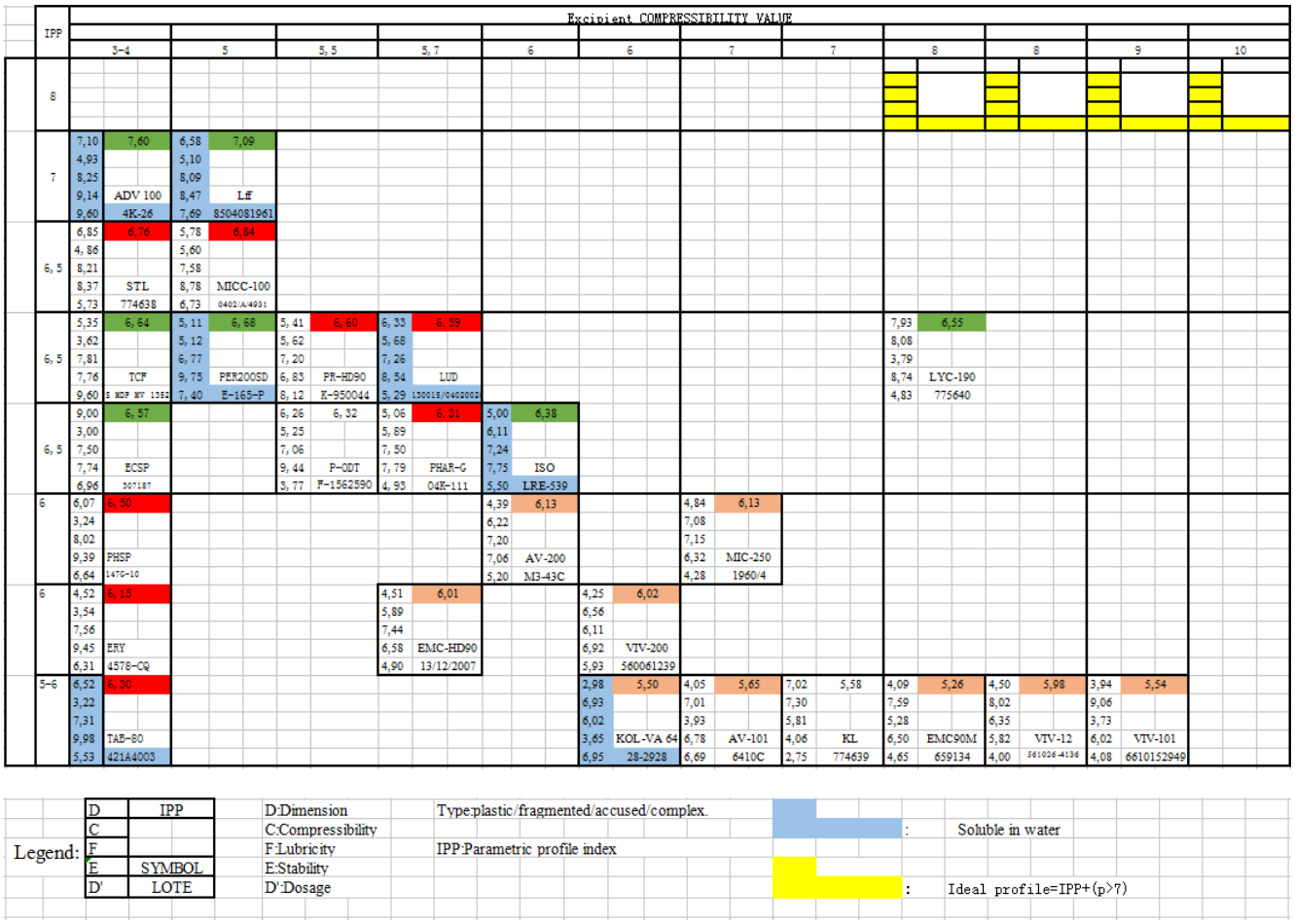

Figure 4. Periodic table of excipients for direct compression

pharmaceutical Quality by design (QbD), and could ideally continue to be perfected.[35]

Except for the 12 basic parameters, there are still other indexes to be developed. As an important disease prevention and control product, the drug efficacy is the most important evaluation standard, and the performance of powder is one of the important factors affecting the bioavailability and efficacy of the drug. The properties of the powder include the mixture uniformity, fluidity of the powder and Disintegration, *etc*.

• The more uniform the mixture, the more uniform the bioavailability, the more stable the curative effect is and the more stable the treatment is. The factors that affect the uniformity of mixing are: particle size, Particle size difference and density difference, Electrostatics and surface energy, *etc*.

• The fluidity of powder is the key factor in the development of solid preparation.

• Disintegration is the most important condition for drug dissolution and therapeutic effect, and the premise of disintegration is that pharmaceutical preparation must be wetted by aqueous solution. And the disintegration of solid preparations is affected by the following factors: porosity, Compression process, Wettability.

4.2 Design of co-processed excipient

Co-processing excipient is a new type of excipient which is different from ordinary single excipient, it is obtained by two or more kinds of excipients through a certain processing procedure.[36] Because there is no chemical reaction in the process, the new co-processing accessory does not have to carry out strict safety tests.[37] Compared with the general physical direct mixture, the co-processing excipient is a kind of functional material with better physical properties, and its various physical indexes are better than the single material or ordinary mixture, which greatly improves the cost effectiveness. At present, excipient co-processing technology mainly includes melting granulation, spray drying and so on.[38,39] However, the use of co-processing excipient is limited by its fixed proportion, and the fixed proportion of excipient is not the best proportion in preprepara-

tion.[40]

The SeDeM Expert System provides an intuitive spectrum of powder properties. The excipients were characterized by SeDeM Expert System, and the defects of the excipients, such as poor fluidity, were studied according to the characterization atlas. The related treatment schemes, such as airflow crushing, were designed, and then the processed excipients were re-characterized by SeDeM Expert System. Study the changes after processing. For the design of co-processing excipients, the complementary excipients can be selected as co-processed excipients according to SeDeM Diagram. After processing and mixing, the co-processing excipients can be characterized by SeDeM Expert System and verified by direct pressure experiments. Combined with SeDeM to design co-processing accessories can reduce unnecessary work and time. According to the SeDeM Expert System, several kinds of co-processed excipients are designed, and the database of co-processing excipients is established so as to select the proportion of excipients needed by different prescriptions.

5 Conclusions

With the wide use of DC technology in pharmaceutical industry, it is important to use a more convenient method to analyze API and excipients and their mixtures which can be compressed directly. Through the summary and analysis above, SeDeM Expert System can be used to analyze and correct the direct compressibility of various kinds of drug powder, and it can be used in the study of different formulations, which can directly reflect the properties of powder science.

At present, the API and excipients of different batches or different kinds, different manufacturers, different chemical family excipients have been characterized by SeDeM Expert System, and the differences of powder properties between them have been analyzed. However, the SeDeM system is not particularly complete. With the continuous emergence of problems encountered in the experiment, the SeDeM Expert System should be improved accordingly.

6 Conflict of interests

The Authors declare they have no conflict of interest.

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