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Review Article

SeDeM in Preformulation of Solid Oral Dosage Form: A Review

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Abstract

The aim of this review is to describe the available method used to check suitablity of API & Excipient for direct compression. Optimization studies can be done in terms of physcal properties like flow of API & Excipients. The SeDeM (Secure Development Method) system is also termed as tool for the galenic characterization of excipients with respect to their suitability for direct compression. It provide an index of good compressibility (ICG) of material indicating its aptitude to be compressed by direct compression.In this method excipients were analysed by experimental studies of SeDeM parameters and represented graphicaly (SeDeM Diagram) to determine whether they are suitable for direct compression or not. This method has factors & mathematical equation to identify the best excipient and the optimum amount to be used in the formulation using different properties of excipients. The SeDeM method is effective tool for development of tablets by direct compression. The application of SeDeM expert system enables selecting excipients with in order to optimize the formula in the preformulation and formulation studies.

Keywords: *SeDeM, Secure Development Method, Optimization Tool, Direct Compression Preformulation Studies*

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Introduction

In formulation of pharmaceutical solid dosage it is important not only have robust formulation but also the process feasibility. Various challanges occurs during the development including issues related with physical property of the excipient and API. In Pharmaceutical industry direct compression technique is widely used due to its costeffectiveness and less time require ability for development. But their are some physical attributes of API & Excipients which limits the secure development using direct compression method. In a general practice API whoes flow is poor restricts smooth and comfortable direct compression process, which yeilds variation in QC as well as chemical analyis of developed dosage form in terms of variation in assay, disso etc. This problem my be overcome by employing flow aid in the powder blend or mixture in form of glidant, antiadherant and lubricants. Working of such flow aids are depend upon the % concentration of use as some flow aids are effective only with limited concentration. Like colloidal silicon dioxide its effective conc is upto 2% only, if its used more than 2% then condition may get reverse.

Therefore its little bit big challange in front of the formulator or developer to overcome such limitation. Here the SeDeM methodology is useful it is applied in preformulation and formulation studies specifically in solid dosage forms. This system shows the physical profile of powdered substances (APIs and excipients) used to formulate drug product[1]. By determining whether powders is suitable for direct compression, the SeDeM profile will highlight the advantages and gaps of those powdered substance to be used in direct compression, this system works on whether the direct compression method is suitable or not. This expert systems identifies the gap or charecteristics that requires any amendment so as to develop robust formulation.

Need of SeDeM Prediction Tools

In preformulation studies every experiment is done in view of checking the feasibility of API with inteded excipients so as to get judge wether the current selected combnation or type of excipient is suitable to form pharmaceutical dosage form with reproduciblity and robustness. SeDeM is the galanic method at preformulation level it avoids extra experimentation and facilitating the process of formulation development. Moreover it can be applied to evaluate reproducibility of powder preparation process[4] SeDeM expert system is based upon ICH guidelines comprised of 12 parameters divided into six factors, covering all the characteristics related to flow, compressibility and disintegration behavior of powder.

Nowadays the development of dosage form is strictly in line with complying all the requirents of regulatory agency, where each stages and component is to be justified so as to proove product developed in scientific ways. SeDeM graphical representation makes easier to understand the deficiencyof powder charecteristics and amount require to mask the deficiency so as to get good powder charecterisitcs interms of flow and compressilbity.

SeDeM Tests & Experimental Procedures

The parameter examins by SeDeM expert system are related to the dimesions, compressiblity, flowability, lubricity and stability. These 12 tests are described as below[2]

1) Bulk density (Da)

Bulk density was calculated in accordance with the method described in section 2.9.15 of European Pharmacopoeia. The total volume in bulk density measurements included particle volume, inter-particle void volume and internal pore volume.

2) Tapped density (Dc)

Dc was calculated in accordance with the method described in Section 2.9.15 of European Pharmacopoeia . It was determined by applying a controlled packing force to the sample and included the interstitial volume and pore volume in its calculations. Graduated cylinder was employed for density measurements and the volume taken was the value obtained after 2500 strokes using a settling apparatus.

3) Inter-particle porosity (Ie)

The inter-particle porosity of the drug powder was calculated by the following equation

Ie = Dc n Da/ Dc X Da

4) Carr index (IC %)

It was computed from Da and Dc using the following equation

IC = (Dc n Da/ Dc) ◊ 100

5) Cohesion index (Icd)

The cohesion index was determined by directly compressing the drug powder under study using an eccentric press. The hardness (N) of the obtained tablets was determined andthe mean hardness was calculated.

6) Hausner ratio (IH)

This was calculated from Da and Dc using the following expression IH = Dc/Da.

7) Angle of repose (α)

It is the three dimensional angle formed by cone like pile of the material during the determination. The angle of the cone formed was calculated after the product was passed through a funnel with the following dimensions: funnel height 9.5 cm, upper diameter of spout 7.2 cm, internal diameter at the bottom, narrow end of spout 1.8 cm. The funnel was placed on a support at 20 cm from table surface, centered over a millimeter- grid sheet on which two intersecting lines were drawn, crossing at the Centre. The narrow end of the funnel spout was plugged and the funnel was filled with the product under study until it was flushed with the top end of the spout when smoothed with a spatula.

Thereafter, the plug was removed and the powder was allowed to fall onto the millimeter sheet. The radius of the cone base was measured with a slide caliper and the mean value (r) was calculated. Additionally, the cone height (h) was measured and the angle tangent value (α) of the cone was calculated employing the following equation: tan α = h/r

8) Flowability (tn)

The flow rate described herein as flowability was determined in accordance with the method described in Section 2.9.16-2 of European Pharmacopoeia (12) as the time for a fixed amount of powder to flow through a glass tunnel with 0.85 cm orifice diameter. It was expressed in seconds and tenths of a second per 100 grams of sample, with the mean value of three determinations always being taken.

9) Loss on drying (%HR)

This is determined by the loss on-drying test carried out in accordance with General method 2.2.32 in European Pharmacopoeia[8]. Excipient PEO was dried in a convection oven at 105°C ± 2°C until a constant weight is obtained.

10) Hygroscopicity (%H)

The hygroscopicity of a powder is its equilibrium moisture content after being exposed to air humidity under given conditions. It was determined by calculating the increase in sample weight after being kept in a humidifier at ambient relative humidity of 76% ± 2% and a temperature of 22°C± 2°C for 24 h.

11) Percentage of particles measuring < 50 µ (%Pf)

Particle size was determined by means of the sieve test in accordance with the General method 2.9.12 of European Pharmacopoeia (14) and was expressed as the % of particles that pass through a 0.05 mm sieve When vibrated for 10 min at speed 10 using a sieve vibrator.

12) Homogeneity index (Iθ)

The method for determination of Iθ was based on General method 2.9.12 of European Pharmacopoeia[9] for determining particle size by means of the sieve test. The grain size of a 100 g sample was determined by submitting a sieve stack to vibration for 10 min at the speed 10 using a sieve vibrator. Sieve sizes used were: 0.355, 0.212, 0.100 and 0.05 mm. The percentage of product retained in each sieve and the quantity that passes through the 0.05 mm sieve were calculated. The percentage of fine particles (< 50 µ) determined previously in a separate operation was considered. The following equation was then applied to the data obtained:

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

Where,

Iθ = relative homogeneity index; Fm = percentage of particles in the majority range;

Fm-1 = percentage of particles in the range immediately below the majority range;

Fm+1 = percentage of particles in the range immediately above the majority range;

n = order number of the fraction under study, within a series, with respect to the majority fraction;

dm = the mean diameter of particles in the majority fraction;

dm-1 = the mean diameter of particles in the fraction of the range immediately below the majority range;

dm+1 = mean diameter of the particles in the fraction of the range immediately above the majority range.

Furthermore, to establish whether or not the powder under study is acceptable for direct compression, under given mathematical indices are calculated for both CfA and PCM based on SeDeM diagram.

$$\text{Parameter index (IP)} = \frac{\text{No of parameters having } r \geq 5}{\text{Total No of Parameters}}$$

Acceptable limit is when IP ≥ 0.5 Parameter profile index (IPP) = Mean r of all the parameters Acceptable limit is when IPP ≥ 5 Good compression index (GCI) = IPP x f

Where, f is a reliability factor and f = polygon area / circle area Acceptable limit is when IPP ≥ 5

Table 1: Test of SeDeM with unit & Equations

Incidence Factor	Parameter (Symbol)	Unit	Equation
Dimensions	Bulk Density (Da)	gm/ml	Da= P/Va
	Tapped Density (Dc)	gm/ml	Dc= P/Vc
Compressibility	Interparticle porosity (Ie)	-	Ie= DC-Da/Dc x Da
	Carr index (Icd)	%	IC = (Dc-Da/Dc)
	Cohesion index (IC)	N	Experimental
Powder Flow	Hausner Ration (IH)	-	IH=Dc/Da
	Angle of repose (α)	-	A =$\tan^{-1}$h/r
	Flowability (t^n)	S	Experimental
Stability	Loss on Drying (% LOD)	%	Experimental
	Hygroscopicity (%H)	%	Experimental
Lubricity	Particles <50 m (%Pf)	%	Experimental
	Homogeneity index (IΘ)	-	Eq. (1)

Significance of Methods

Each test plays and important role as a prediction tool, cumulatively all tests signifies their performance interms of predicting the deificincy. In Table 2 all SeDeM tests and their significance are described[3]

Table 2: SeDeM Tests & Their Significance

Parameter	Significance
Bulk Density (Da) Tapped Density (Dc)	The Tapped density and Bulk density measurements are used in calculating other vital parameters depicting flow characteristics of powders.
Interparticle porosity (Ie)	If the particles are smaller, sticky, or of extreme shape (e.g., fibrous), their porosities may be considerably greater and may constitute the non-free flowing powders
Carr index (Icd)	Carr index or compressibility index is the indirect measure of various powder characteristics viz. bulk density, size and shape, surface area, moisture content and cohesiveness of the material
Cohesion index (IC)	Cohesion index reflects the stability of the rapid particular rearrangements of powder also indicating compaction suitability of the granules
Hausner Ration (IH)	The Hausner ratio is a number that is correlated to the flow ability of a powder or granular material
Angle of repose (α)	Angle of repose is a characteristic related to inter-particulate friction or resistance to the movement between the particles
Flowability (t^n)	Powder flow characteristics are commonly investigated under gravity loading conditions. The flow rate of a material depends upon many factors, some of which are particle related and some are related to process
Loss on Drying (% LOD)	The loss on drying is a measure of the amount of water and volatile matters in a sample when the sample is dried under specified conditions. Hence, LOD could be a determining factor in powder flow studies
Hygroscopicity (%H)	High hygroscopicity is undesirable for many reasons including handling problems, requirement of special storage conditions, and chemical and physical stability problems
Particles <50 m (%Pf)	Particle size plays an extremely important role in the homogeneity of powder blends, rheological and compression problems occur when the percentage of fine particles in the formulation exceeds 25%.
Homogeneity index (IΘ)	Homogeneity index is a simple scoring tool that quantifies dose homogeneity in the target volume. It is therefore used to evaluate and compare the dose distributions

Determination of Acceptable Limits & Conversion of limit in Factors

On the basis of experimental tests & Handbook of excipient described values certain limits are set Table 3 after performing tests on powder the values obtained are convertedin the factors shown in the table to obtain readius value.[2]

Table 3: Limit values and conversion factors of SeDeM parameters

Incidence Factor	Parameter (Symbol)	Limit Value	Conversion factor applied
Dimensions	Bulk Density (Da)	0-1	10v
	Tapped Density (Dc)	0-1	10v
Compressibility	Interparticle porosity (Ie)	0-1.2	10v/1.2
	Carr index (Icd)	0-50	10-(v/5)
	Cohesion index (IC)	0-200	v/20
Powder Flow	Hausner Ration (IH)	3-0	10-(10v/3)
	Angle of repose (α)	50-0	10-(v/5)
	Flowability (t^n)	20-0	10-(v/2)
Stability	Loss on Drying (% LOD)	10-0	10-v
	Hygroscopicity (%H)	20-0	10-(v/2)
Lubricity	Particles <50 m (%Pf)	50-0	10-(v/5)
	Homogeneity index (IΘ)	0-0.02	500v

Graphical Represetation of SeDeM Diagram

The SeDeM Diagram indicates the characteristics of the product and of each of parameter that determines whether product is suitable for direct compression. In this case, the SeDeM Diagram is made up of 12 parameters, thus forming regular 12- sided polygon when all radius values are 10 Fig. 1. This SeDeM diagram drawn by connecting the radius values with linear segments. The results obtained from the earlier parameter calculations and conversions are represented by the radius. The figure formed indicates the characteristics of the product and of each parameter that determines whether the product is suitable for direct compression[8]

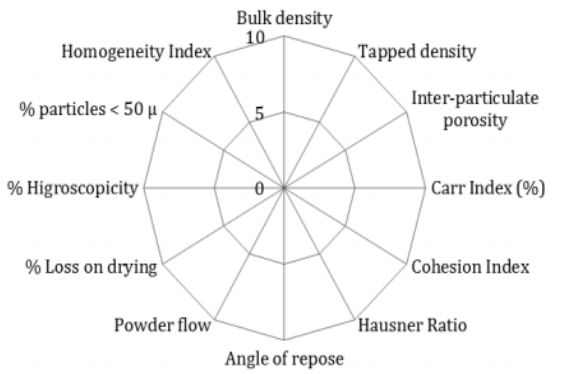

Fig. 1: SeDeM Diagram

Application of SeDem

On the basis of the radius corresponding to the SeDeM Diagram, the parametric profile was calculated. This value implies suitablity for direct compression. Experimental determination of the parameters of the SeDeM method for a range of APIs and excipients allows definition of their corresponding compressibility profiles and their subsequent mathematical treatment and graphical expression[2]

The mathematical equation can be applied to the 5 parameters (dimension, compressibility, flowability / powder flow, lubricity / stability lubricity / dosage) considered deficient by theSeDeM system. The mathematical equation is applied to correct a deficient parameter of the API. The equation proposed (Equation 1) allows calculation of the amount of excipient required to compress the API on the basis of the SeDeM radius considered minimum for each parameter of incidence that allows correct compression.[12]

$$CP = 100 - \frac{[RE-R]}{[RE-RP]} X\ 100 \quad \ldots\ldots (1)$$

Where:

CP = % of corrective excipient

RE = mean-incidence radius value (compressibility) of the corrective excipient

R = mean-incidence radius value to be obtained in the blend

RP = mean-incidence radius value (compressibility) of the API to be corrected

The unknown values to be replaced by the calculated ones required for each substance in order to obtain radius value R = 5 (5 is the minimum value considered necessary to achieve satisfactory compression). For example, if a deficient compressibility parameter for an API requires correction, Equation 1 is applied by replacing the terms RE and RP with the values calculated for each substance with the purpose to obtain a R=5, thus obtaining the optimal excipient to design a first drug formulation and the maximum amount required for a comprehensive understanding of the proposed formula. From this first formulation. If the API has deficient compressibility parameters (<5), it is mixed with an excipient with a satisfactory compressibility parameter (>5), thereby correcting the deficiency. The excipient that shows the smallest

amount to correct this parameter should be used. The amount of excipient is determined by the mathematical equation of the SeDeM system (Equation 1).

To better understand the SeDeM system, the graphical representations of the profiles of the API and the excipient can be superposed. Figure 3 shows how the deficiencies of an API would be compensated when formulated. The green line corresponds to the excipient that theoretically provides the final mixture the characteristics to be compressed. In this way, the information provided by the SeDeM system allows the formulator to start working with excipients that have a high probability to provide suitable formulations, thus reducing the lead time of formulation.

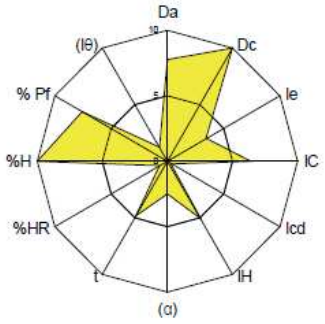

Fig.2: Example of API processed through SeDeM Parameter

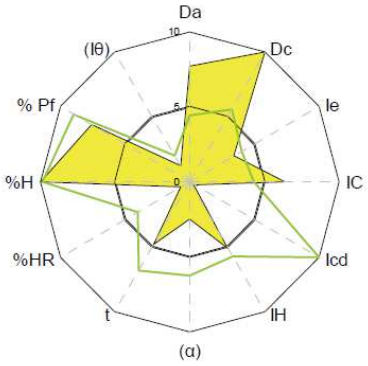

Fig.3: Green lines indicates correction of deficient API

SeDeM Diagram to differentiate excipients of the same functional type[2]

This Expert system allows differentiation between excipients from the same functional type, for example disintegrants or diluents. In the former, the SeDeM characterization provides the information required to predict the difficulties encountered for compression. The characterization of several binder or disintegrants using the SeDeM technique, where the differences between each one in relation to their major or minor compression capacity are shown, although all are used because of their disintegrant function

SeDeM – ODT[2]

A new system by SeDeM in the design and development of ODT has been started where their are 15 parameters insted of 12 previously applied parameters, and the application procedure is same as described above newly introduced parameters are as below

Table 4: Newly introduced parameters for SeDeM – ODT Expert System

Factor	Parameter	Limit value	Radius
Disintegrability	Effervescence	0-5 (Minutes)	10-0
	Disintegration time with Disc	0-3 (Minutes)	10-0
	Disintegration time without disc	0-3 (Minutes)	10-0

Conclusion

The SeDeM system is can be used for cross verification of the reproducibility of manufacturing standards between batches of the same raw material, with established data the SeDeM profile informs about the advantages and gaps of those powdered substance to be used in direct compression. It gives accurate predictions and prospective judgment about material properties and response of the material was same as predicted by the SeDeM expert system intended to be used in formulation. This system is a useful tool because, in addition to considering the type of components, it also provides recommendations on intrinsic properties, such as the characteristics and morphology of the particles. This system is and expert system which is of high use in the preformuation studies, this system can be utilized for granulation method too, granules obtained with different machines and different parameters can be processedwith SeDeM System to obtain best suitable profiles for compression process. It reduces no of trials and lead to succesful compression by providing thee predicion of behavious of powdered substance used in th formulation. It identifies best suitable excipient and calculating % requires for correction of deficiencies of behaviour of API to prepare perfect scientific blend. Application of this system allows to avoid use of unecessary excipients and reduces time in the development finaly it contributes development as per the regulatory agencies current requirement of QBD (Quality by Design).

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