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A Review On: SeDeM Expert System in Formulation Development of Pharmaceutical Forms

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ABSTRACT:

The SeDeM system is a useful 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 Different excipients were analysed by experimental studies of SeDeM parameters and graphical expression (SeDeM Diagram) to determine whether they were suitable for direct compression. Mathematical equation and properties of excipients were used to identify the best excipient and the optimum amount to be used in the formulation. The results confirm that 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.

KEY WORDS: SeDeM Expert system, Direct Compression, Bulk Density (Da), Tapped Density (Dc), Interparticle Porosity (Ie), Carr Index(IC), Angle of Repose (α).

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INTRODUCTION: [1, 2, 3]

SeDeM known as **"Sediment delivery model"**. SeDeM expert system is a new galenic system to be applied in tablet preformulation and formulation studies of medicines specifically in solid dosage forms. It is used for an evaluation of critical quality attributes having an impact on the final product. The system informs on the physical profile of powdered substance (API and excipients) used for formulation. It provide information about suitability of active ingredients and excipient, in powder form, for direct compression. This information indicates the degree to which the substances can be successfully compressed by means of direct compression technology. SeDeM system allow to detect the powder properties need to be improved to facilitate the formulation of the end product for direct compression. Therefore this system provides information that will ensure the robust design of formulation in final product. The method is based on the selection and application of several parameters that the formulation must fulfil to ensure a successful tablet elaborated by direct compression.

Parameters examined by the SeDeM method

SeDeM uses 12 parameters to examine whether a powder is suitable for direct compression.

• Bulk density (Da)

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

These parameters are grouped into five factors on the basis of the physical characteristics of the powder and the functionality of the drug:

- **Dimensional Parameter**: Bulk density (Da) and Tapped density (Dc). These affect the size of the tablet and its capacity to pile up. In addition, these tests are used in the calculus of other mathematical indexes for the determination of the compression parameter.
- **Compressibility Parameter**: Inter-particle porosity (Ie), Carr index (IC) and Cohesion index (Icd). These affect the compressibility of the powder.
- **Flowability/Powder Flow Parameter:** Hausner ratio (IH), Angle of repose (α) and Flowability (t"). These influence the flowability of the powdered substance when compressed.
- **Lubricity/Stability Parameter**: Loss on drying (%HR) and Hygroscopicity (%H). These affect the lubricity and future stability of the tablets.
- **Lubricity/Dosage parameter**: % Particles < 50 µm and Homogeneity Index. These influence the lubricity and dosage of the tablets.

The following table 1 shows the 12 parameters with the abbreviations, units, formulas and incidence on compression.

SeDeM parameters are described below.

- **Bulk density (Da):** It is the ratio of total mass of powder to the bulk volume of powder. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/ cm3 and calculated by following formula,
Bulk Density (Da) = Weigh of powder/Bulk volume

Table 1. Parameter and equation used by the SeDeM system.

Incidence factor	Parameter	Symbol	Unit	Equation
Dimension	Bulk Density	Da	g/ml	Da = P/Va
	Tapped Density	Dc	g/ml	Dc =P/Vc
Compressibility	Inter-particle porosity	Ie	-	Ie = Dc – Da/Dc*Da
	Carr Index	Ic	%	IC = (Dc – Da/Dc) 100
	Cohesion Index	Icd	N	Experimental
Flowability/ Powder flow	Hausner Ratio	IH	-	IH = Dc/Da
	Angle of Repose	(α)	°	tg α = h/r
	Powder Flow	t''	s	Experimental
Lubricity/ Stability	Loss on Drying	%HR	%	Experimental
	Hygroscopicity	%H	%	Experimental
Lubricity/ Dosage	Particles < 50 µm	%Pf	%	Experimental
	Homogeneity index	(Iθ)	-	*Iθ = Fm / 100 + Δ Fmn

- **Tapped density (Dc):** It is the ratio of total mass of powder to the tapped volume of powder. Volume was measured by tapping the powder for 500, 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued for until the difference between successive volumes is less than 2%. It is expressed in gm/ cm3 and calculated by following formula,
Tap Density (Dc) = Weigh of powder/Tap volume

- **Inter-particle porosity (Ie):** It is defined as pore space located between grains or crystals and is not significantly larger that than the particle. inter-particle porosity of the powder is calculated by the following formula,
Ie=Dc-Da/Dc×Da

- **Carr index or Compressibility index (IC%):** The compressibility index measures the propensity of

powder to be compressed. The packing ability of drug was evaluated from change in volume, which is due to rearrangement of packing occurring during tapping. It is indirectly related to the flow rate, cohesiveness and particle size. It is calculated by following formula,

IC=(Dc-Da/Dc)100

- **Hausner ratio (IH):** It is the ratio of tapped density to the bulk density. It is an indirect index of ease of powder flow. It is calculated by following formula,

  IH=Dc/Da

- **Angle of repose (α):** It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. The accurately weighed powder blend was taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following formula,

  tan(α)=h/r.

- **Flowability (t"):** Flowability is intended to determine the ability of divided solids to flow vertically under defined conditions. It indicates the flow property of powder. It is expressed in seconds and tenths of a second per 100 grams of sample, with a mean value of three measurements.

- **Loss on drying (%HR):** Loss on drying (LOD) test is designed to measure the amount of water in the sample, when sample is dried under specified conditions. The sample is dried in an oven at 105 °C, until a constant weight of the sample is obtain.

- **Hygroscopicity (%H):** In hygroscopicity the sample is kept in the humidifier at a relative humidity of 76% (±2%) and a temperature of 22°C± 2°C for 24 h. Then determine the the percentage increase in sample weight.
- **Paticle size < 50 µm (%Pf):** Particle size of powder is determined by the sieve test. In this test 100 g of accurately weighed sample is pass through the a 0.05-mm sieve where it is vibrated for 10 min at speed 10 and determine the % of particle that pass through the sieve.

- **Homogeneity index (Iθ):** It is used to determine particle size by sieve test. In this test 100g of accurately weighed sample is pass through 0.355 mm, 0.212 mm, 0.100 mm and 0.05 mm sieve where it is vibrated for 10 min at speed 10. The percentage of product retained in each sieve is calculated and the amount that passes through the 0.05mm sieve is measured. The percentage of fine particles (<50 µm) (%Pf) was determine as described above. The following equation is then applied to the data obtained.

$$*I\theta = \frac{Fm}{100+(dm-dm-1)Fm-1+(dm+1-dm)Fm+1+(dm-dm-2)Fm-2+(dm+2-dm)Fm+2+\ldots.+(dm-dm-n)Fm-n+(dm+n-dm)Fm+n}$$

Where:

- Iθ, Relative homogeneity index. Particle-size homogeneity in the range of the fractions studied;
- 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 studied under a series, with respect to the major fraction;
- dm, mean diameter of the particles in the major fraction;
- dm−1, mean diameter of the 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.

When the parameters of the SeDeM Diagram have been established, we determined the acceptable numerical limit values for each of the 12 study parameters and each Diagram radius was calculated by applying the equations in Table 1 to convert the values obtained into radii (r). All these values are shown in Table 2.

The following table 2 shows the Limit value accepted for the SeDeM Diagram parameters and conversion of limit for each parameters into radius values (r).

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

Incidence factor	Parameter	Limit (v)	Radius (r)	Factor applied to v
Dimension	Bulk Density	0-1 g/ml	0-10	10v
	Tapped Density	0-1 g/ml	0-10	10v
Compressibility	Inter-particle porosity	0-1.2	0-10	10v/1.2
	Carr Index	0-50 (%)	0-10	v/5
	Cohesion Index	0-200 (N)	0-10	v/20
Flowability/Powder flow	Hausner Ratio	3-1	0-10	(30-10v)/2
	Angle of Repose	50-0 (°)	0-10	10 – (v/5)
	Powder Flow	20-0 (s)	0-10	10 – (v/2)
Lubricity/Stability	Loss on Drying	10-0 (%)	0-10	10 – v
	Hygroscopicity	20-0 (%)	0-10	10 – (v/2)
Lubricity/Dosage	Particles < 50 µm	50-0 (%)	0-10	10 – (v/5)
	Homogeneity index	0-2 × 10-2	0-10	500v

Graphical representation of SeDeM Diagram[3]

When all radius values are 10, the SeDeM Diagram takes the form of a circumscribed regular polygon drawn by connecting the radius values with line segments. The results obtained from the earlier parameter calculation and conversion are represented by the radius.

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 (Figure 1).

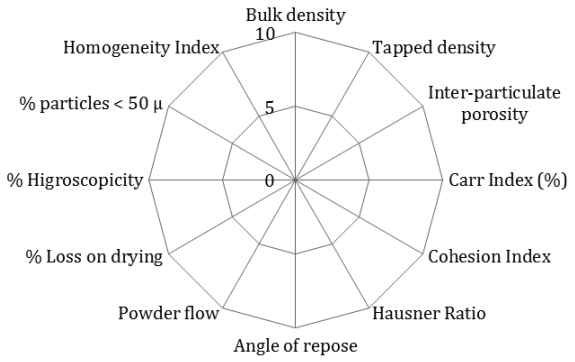

Figure 1. The SeDeM Diagram with 12 parameters.

Acceptable limits for Indexes

- To determine whether the product is suitable for direct compression using a numerical method, the following indices are calculated based on the SeDeM Diagram as follows.

$$\text{Parameter index (IP)} = \frac{\text{no of P} \geq 5}{\text{no of Pt}}$$

- Where,
  No. p ≥ 5 : Indicate the number of parameters whose value is equal to or higher than 5
  No. Pt : Indicate the total number of parameters studied
- Parameter Profile Index (IPP) = Average of (r) all parameters
  Average (r) = mean value of the parameters calculated
  The acceptability limit would correspond to: IPP = means (r) = 5
- Good Compressibility Index (ICG) = IPP × f =5
  Where,
  f = Reliability factor = Polygon area / Circle area
  The acceptability limit would correspond to: ICG = IPP × f = 5
  For 12 parameters f value = 0.952

Application of SeDeM System[7]

1. Determination of the suitability of an API to be subjected to direct compression technology.

The SeDeM method is used to characterize an active product ingredient in powder form and to determine whether it is suitable for direct compression, applying the profile to the SeDeM Diagram. We measured the 12 parameters proposed in the SeDeM method. To obtain the indices of acceptance or qualification for formulation by direct compression, the formulas corresponding to the parametric index were applied from the numerical results of the radius. On the basis of the results of the radius corresponding to the SeDeM Diagram, the parametric profile was > 5. This value implies that material is suitable for direct compression.

2. Application of the SeDeM method to determine the amount of excipient required for the compression of an API that is not apt for direct compression.

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 allows calculation of the amount of excipient required to compress the API on the basis of the SeDeM radius considered minimum (5) for each parameter of incidence that allows correct compression.

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

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

3. Application of the SeDeM system to the quality control of batches of a single API or excipient used for direct compression.The SeDeM system is also apt for verification of the reproducibility of manufacturing standards between batches of the same powdered raw material (API or excipient). Indeed, superposing the SeDeM Diagrams of each batch, the degree of similarity or difference between the same API on the basis of the established parameters can determine its appropriateness for compression.

4. Application of the SeDeM method to differentiate the excipient in the samechemical family. The SeDeM system also allows differentiation between excipients of the same chemical family but that differ in physical characteristics. These characteristics will determine their use in a formulation for direct compression of a given API.

5. Application of the SeDeM Diagram to differentiate excipients of the same functional type.Also, the SeDeM Expert system allows differentiation between excipients from the same functional type, for example disintegrants or diluents.

6. The new model SeDeM-ODT to develop orally disintegrating tablets by directCompression. This innovative tool is the new SeDeM-ODT model which provides the Index of Good Compressibility & Bucodispersibility (IGCB index) obtained from the previous SeDeM method. The IGCB index is composed by 6 factors. Moreover, the index simultaneously indicates whether these tablets are suitable as bucodispersible tablet (disintegration in less than 3 minutes). The new factor, disgregability has three parameters that influence this parameter.

Factor	Parameter	Limit value(v)	Radius
Disgregability	Effervescence	0-5 (minutes)	10-0
	Disintegration Time with disc (DCD)	0-3(minutes)	10-0
	Disintegration Time without disc (DSD)	0-3(minutes)	10-0

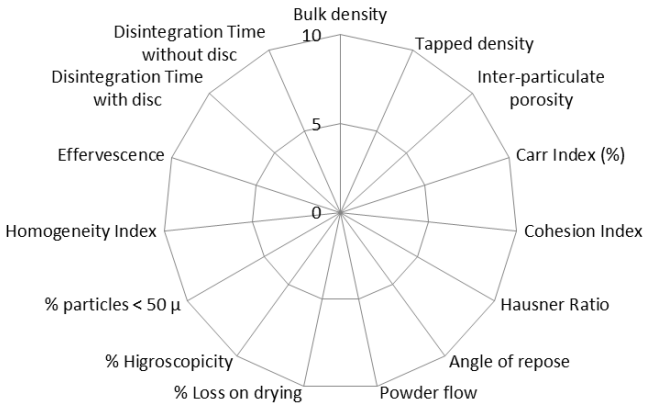

Figure 2. SeDeM-ODT Diagram

CONCLUSION

The SeDeM system is a useful tool for the galenic characterization of excipients with respect to their suitability for direct compression. It gives accurate predictions about material behavior and response of the material was same as predicted by the SeDeM expert system. It provides a physical profile of API and excipients 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. We propose that given the accuracy of the information provided by this system, formulations will have a higher probability of being successfully compressed. This system also reduces the number of trials at a pre formulation level to get produced by direct compression. A SeDeM mathematical model is established that provides for identifying the best excipient and calculating the amount of this excipient required for the direct compression of an API, based on the characteristics modelled in the SeDeM Diagram. This manufacturing procedure offers many advantages from a production perspective. In addition SeDeM has the advantage of providing formulation with the lowest amount of excipients as it combines the API with only one excipient and the standard formula of lubricants, thus avoiding the used of unnecessary excipients, such as diluents, binders and agglutinants. The information given by the SeDeM system contributes to a Quality by Design Development.

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