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PREFORMULATION STUDIES FOR DIRECT COMPRESSION SUITABILITY OF CEFUROXIME AXETIL AND PARACETAMOL: A GRAPHICAL REPRESENTATION USING SeDeM DIAGRAM

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Abstract: The direct compression suitability of active pharmaceutical ingredients could be studied by SeDeM diagram method. Cefuroxime axetil (CfA) and paracetamol (PCM) were employed for SeDeM studies as these powders are well-characterized and known to be particularly difficult with respect to flowability and compactibility. Twelve different selected pharmacotechnical parameters were determined experimentally and were treated mathematically for being expressed in graphic representation as SeDeM diagram. Parameter index, parameter profile index and good compression index were calculated for both the selected drugs. Good compression index was found to be 2.19 and 1.36 for CfA and PCM, respectively, indicating poor direct compression characteristics of the selected drugs. The results from this SeDeM diagram method are in line with the previously reported studies where it was established as a reliable method for preformulation studies and as a quality control tool for studying batch-to-batch reproducibility of API's. Furthermore, it once again established the notion that blending poorly compressible drugs with suitable ingredients followed by SeDeM studies could be used as method for identifying best excipient and calculating maximum amount of excipient required for direct compression of API.

Keywords: direct compression, cefuroxime axetil, paracetamol, powder flow, SeDeM diagram

The SeDeM diagram is a novel and reproducible method for application to preformulation studies of tablets (1). The suitability of a powder (active or inactive pharmaceutical ingredient) for direct compression could be studied using this method. Moreover, this method could be seen as a useful tool for studying the reproducibility of a process used for the preparation of powdered substance. Certain powder characteristic parameters are taken into consideration for development of SeDeM diagram. These selected parameters are consequently studied and analyzed statistically to ascertain the applicability of the method. Furthermore, to ensure reproducible powder quality, appropriate specifications are established for different characterization parameters. These specifications should also be used to set an acceptable range for each parameter adopted in accordance with the SeDeM method, with the aim of providing valid specifications for any powder substance regarding its suitability for direct compression (2, 3).

The SeDeM method is based on the experimental study and quantitative determination of the characterization parameters of powdered substances that provide the necessary information about ability of a substance to be used for direct-compression technology. The considered parameters are as follows: bulk density (Da), tapped density (Dc), interparticle porosity (Ie), Carr index (IC), cohesion index (Icd), Hausner ratio (IH), angle of repose (a), flowability (t^n), loss on drying (%LoD), hygroscopicity (%H), particle size (%Pf) and homogeneity index (Iq).

These parameters were determined by validated experimental methods and processed for fitting into SeDeM diagram method and analyzed for studying suitability of the powder for direct compression. Hence, SeDeM diagram method could be described as mathematical and graphical representation of powder characteristic parameters for studying direct compression suitability of various active and inactive ingredients.

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MATERIALS AND METHODS

Cefuroxime axetil (CfA) and paracetamol (PCM) were supplied as gift samples by Surya Pharmaceuticals Ltd., Chandigarh, India. Calcium carbonate granules were received as gift sample from S. Zhaveri Ltd., Mumbai.

Standard reported pharmacopoeial methods were employed for the determination of various parameters used for the construction of SeDeM diagram.

• Bulk density (Da): Bulk density was calculated in accordance with the method described in section 2.9.15 of European Pharmacopoeia (4). The total volume in bulk density measurements included particle volume, inter-particle void volume and internal pore volume.

• Tapped density (Dc): Dc was calculated in accordance with the method described in Section 2.9.15 of European Pharmacopoeia (4). It was determined by applying a controlled packing force to the sample

Table 1. Various parameters and their respective factors for radius calculations used in SeDeM diagram method.

Parameter (Symbol)	Unit	Equation	Limit value (v)	Radius (r)	Factor applied to v
Bulk density (Da)	g/mL	Da = P/ Va	0–1	0–10	10v
Tapped density (Dc)	g/mL	Dc = P/Vc	0–1	0–10	10v
Interparticle porosity (Ie)	–	Ie = Dc – Da/Dc × Da	0–1.2	0–10	10v/1.2
Carr index (IC)	%	IC = (Dc – Da/Dc)	100 50–0	0–10	10 – (v/5)
Cohesion index (Icd)	N	Experimental	0–200	0–10	v/20
Hausner ratio (IH)	–	IH = Dc/Da	3–0	0–10	10 – (10v/3)
Angle of repose (α)	–	$\alpha = \tan^{-1} h/r$	50–0	0–10	10 – (v/5)
Flowability (t^a)	S	Experimental	20–0	0–10	10 – (v/2)
Loss on drying (%LoD)	%	Experimental	1.5–0[a] 2.5–0[b]	0–10 0–10	10 – (10v/1.5)[a] 10 – (10v/2.5)[b]
Hygroscopicity (%H)	%	Experimental	20–0	0–10	10 – (v/2)
Particles < 50 m (%Pf)	%	Experimental	50–0	0–10	10 – (v/5)
Homogenity index (Iθ)	-	Eq. (1)	0–0.02	0–10	500v

[a] CfA, [b] PCM

Table 2. SeDeM diagram method results of calcium carbonate granules.

Parameter (Symbol)	V1	V2	V3	V	R1	R2	R3	R
Bulk density (Da)	0.552	0.556	0.544	0.551	5.52	5.56	5.44	5.51
Tapped density (Dc)	0.664	0.661	0.655	0.660	6.64	6.61	6.55	6.60
Interparticle porosity (Ie)	0.306	0.286	0.311	0.301	2.55	2.38	2.59	2.51
Carr index (IC)	16.87	15.88	16.95	16.51	6.63	6.83	6.61	6.69
Cohesion index (Icd)	263.2	270.1	271.8	268.4	10.00	10.00	10.00	10.00
Hausner ratio (IH)	1.20	1.18	1.21	1.19	6.0	6.07	5.97	6.02
Angle of repose (α)	22.10	21.75	22.90	22.25	5.58	5.65	5.42	5.55
Flowability (t^a)	8.55	8.01	8.88	8.48	5.72	5.99	5.56	5.76
Loss on drying (%LoD)	0.70	0.73	0.85	0.76	5.33	5.13	4.33	4.93
Hygroscopicity (%H)	0.014	0.018	0.016	0.016	9.993	9.991	9.992	9.992
Particles < 50 μ (%Pf)	0.85	0.92	0.93	0.90	9.83	9.82	9.82	9.82
Homogenity index (Iθ)	0.0042	0.0041	0.0041	0.0041	2.1	2.05	2.05	2.05

Parametric index (IP) = 0.75. Parametric profile index (IPP) = 6.28. Good compression index (GCI) = 5.25

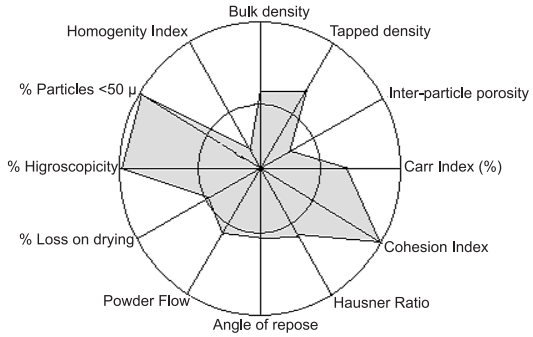

Figure 1. SeDeM diagram for calcium carbonate granules

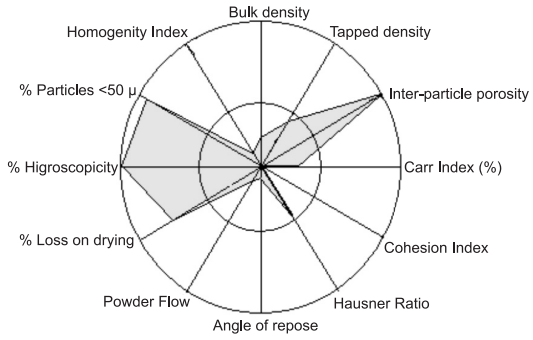

Figure 2. SeDeM diagram for cefuroxime axetil (CfA)

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.

• Inter-particle porosity (Ie): The inter-particle porosity of the drug powder was calculated by the following equation (5):

$$Ie = Dc - Da/\ Dc \times Da$$

• Carr index (IC%): It was computed from Da and Dc using the following equation (6–10):

$$IC = (Dc - Da/\ Dc) \times 100$$

• 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 and the mean hardness was calculated.

• Hausner ratio (IH): This was calculated from Da and Dc using the following expression (6):

$$IH = Dc/Da.$$

• Angle of repose (α) (7–11): 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:

$$\tan \alpha = h/r$$

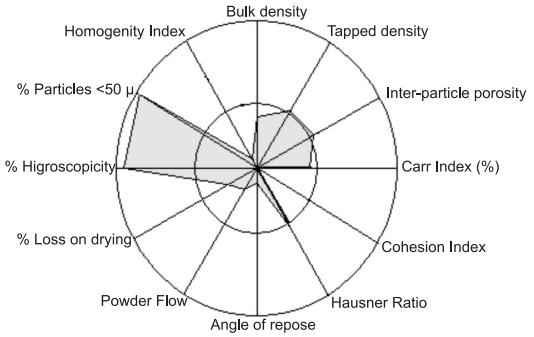

Figure 3. SeDeM diagram for paracetamol (PCM)

• Flowability (t^n): 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.

• 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 (13). Drug samples, paracetamol and cefuroxime axetil, were dried in a convection oven at 105 ± 1°C and 70 ± 1°C, respectively, until a constant weight is obtained.

• 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 ± 2°C for 24 h.

• 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.

• Homogeneity index (Iθ): The method for determination of Iθ was based on General method 2.9.12 of European Pharmacopoeia (14) 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:

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

where Iθ = relative homogeneity index; F_m = percentage of particles in the majority range; F_{m-1} = percentage of particles in the range immediately below the majority range; F_{m+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; d_m = the mean diameter of particles in the majority fraction; d_{m-1} = the mean diameter of particles in the fraction of the range immediately below the majority range; d_{m+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.

$$\text{Parameter index (IP)} = \frac{\text{Number of parameters having } r \geq 5}{\text{Total number of parameters}}$$

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 × f

where f is a reliability factor and f = polygon area / circle area

Acceptable limit is when IPP ≥ 5

RESULTS AND DISCUSSION

Standard pharmacopoeial methods were employed for calculating the experimental value of the parameters selected for preparing SeDeM diagram. The experiments were performed in triplicate to ensure suitability of method and statistically significant results, followed by calculating the mean value of the parameters. As described in Table 1, conversion factors could be applied to the respective parametric values to obtain the radius (r). Experimental value (V1, V2, V3), the mean of experimental values (V) and respective radius values (R1, R2, R3), the mean of radius values (R) of different flow parameters for calcium carbonate granules, CfA and PCM salts are shown in Tables 2, 3 and 4, respectively. These calculated radius values were graphically expressed on a regular Pie-Chart by plotting the radius values. The SeDeM diagrams were then drawn by connecting the radius values with linear segments.

In free flowing powders inter-particulate interactions are less significant and unsettled and tapped densities will be closer in values. In poorly flowing powders inverse is expected. The voidage fractions of tapped and loosely packed powder beds have been known to be related semiempirically to the size distribution, shape, and density of the constituent particles (15). Furthermore, tapped density and bulk density measurements are used in calculating other vital parameters depicting flow characteristics of powders. The bulk density and tapped density for CfA are 0.226 and 0.345 with corresponding radius values 2.26 and 3.45, respectively. The bulk density and tapped density for PCM found to be 0.396 and 0.521 with radius values of 3.96 and 5.21. Calcium carbonate granules showed bulk density and tapped density of 0.551 and 0.660 with 5.51 and 6.60 radius values.

The interparticle porosity in case of CfA, value and radius, 1.63 (13.58), while that of PCM are 0.636 (5.30). Interparticle porosity was found to be 0.301 for calcium carbonate granules with 2.51 as radius value. If the particles are smaller, sticky, or of extreme shape (e.g., fibrous), their porosities may be considerably greater and may constitute the nonfree-flowing powders.

Cohesion index reflects the stability of the rapid particular rearrangements of powder. Cohesion index values in case of both the selected APIs found to be zero indicating no compaction suitability, whereas that of calcium carbonate granules was coming out to be 10, indicating good compaction suitability of the granules.

Carr index or compressibility index is the indirect meaure of various powder characteristics viz. bulk density, size and shape, surface area, moisture content and cohessiveness of the material.

Table 3. SeDeM diagram method results of CfA.

Parameter (Symbol)	V1	V2	V3	V	R1	R2	R3	R
Bulk density (Da)	0.223	0.254	0.202	0.226	2.23	2.54	2.02	2.26
Tapped density (Dc)	0.311	0.376	0.347	0.345	3.11	3.76	3.47	3.45
Interparticle porosity (Ie)	1.58	1.61	1.69	1.63	13.16	13.42	14.08	13.58
Carr index (IC)	35.73	34.84	36.32	35.63	2.85	3.03	2.74	2.85
Cohesion index (Icd)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Hausner ratio (IH)	1.56	1.56	1.54	1.55	4.80	4.80	4.87	4.82
Angle of repose (α)	46.80	47.33	47.61	47.25	0.64	0.54	0.48	0.55
Flowability (t^n)	17	18	18	17.66	1.5	1	1.5	1.16
Loss on drying (%LoD)	0.46	0.42	0.42	0.43	6.94	7.2	7.2	7.14
Hygroscopicity (%H)	0.000	0.089	0.130	0.073	10.00	9.95	9.94	9.96
Particles < 50 μ (%Pf)	1.43	1.40	1.39	1.41	9.71	9.72	9.72	9.72
Homogenity index (Iθ)	0.0031	0.0031	0.0032	0.0031	1.55	1.55	1.60	1.56

Parametric index (IP) = 0.33. Parametric profile index (IPP) = 4.75. Good compression index (GCI) = 1.01

Table 4. SeDeM diagram method results of PCM

Parameter (Symbol)	V1	V2	V3	V	R1	R2	R3	R
Bulk density (Da)	0.393	0.412	0.384	0.396	3.93	4.12	3.84	3.96
Tapped density (Dc)	0.508	0.536	0.519	0.521	5.08	5.36	5.19	5.21
Interparticle porosity (Ie)	0.632	0.634	0.637	0.636	5.26	5.28	5.31	5.30
Carr index (IC)	27.32	28.01	27.65	27.66	4.54	4.40	4.47	4.47
Cohesion index (Icd)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Hausner ratio (IH)	1.37	1.38	1.38	1.38	5.43	5.40	5.40	5.41
Angle of repose (α)	43.62	43.29	43.41	43.44	1.27	1.34	1.32	1.31
Flowability (t^n)	16	16	16	16	2	2	2	2
Loss on drying (%LoD)	1.86	1.81	1.79	1.82	2.56	2.76	2.84	2.72
Hygroscopicity (%H)	0.58	0.70	0.62	0.63	9.71	9.65	9.69	9.68
Particles < 50 μ (%Pf)	0.82	0.77	0.95	0.84	9.83	9.84	9.81	9.83
Homogenity index (Iθ)	0.0014	0.0017	0.0013	0.0015	0.70	0.85	0.65	0.75

Parametric index (IP) = 0.50. Parametric profile index (IPP) = 4.22. Good compression index (GCI) = 0.69

Table 5. Scale of flowability.

Flow Character	Carr index	Hausner ratio	Angle of repose [°]
Excellent	≤ 10	1.00–1.11	25–30
Good	11–15	1.12–1.18	31–35
Fair (aid not needed)	16–20	1.19–1.25	36–40
Passable (may hang up)	21–25	1.26–1.34	41–45
Poor (must agitate/vibrate)	26–31	1.35–1.45	46–55
Very poor	32–37	1.46–1.59	56–65
Very, very poor	> 38	> 1.60	> 66

Experimental value of Carr index is 16.51, 35.63 and 27.66 for calcium carbonate granules, CfA and PCM, respectively. The calculated radius values of Carr index were 6.69, 2.85 and 4.47 for calcium carbonate granules, CfA and PCM, respectively. The radius values are less than 5 for the selected API, which is an indication of poor flow and in turn, low compressibility for both the drugs. SeDeM results of Hausner ratio values for CfA and PCM, respectively, 1.55 (radius 4.82) and 1.38 (radius 5.41) were at the edge of acceptible range of radius value. The flow character of both the APIs was found to be poor and very poor as per the generally accepted scale of flowability (Table 5). SEDEM results of Hausner ratio for calcium carbonate were well acceptable (Table 2).

Angle of repose is a characteristic related to interparticulate friction or resistance to the movement between the particles. Average value of angle of repose is coming to be 47.25 and 43.44 for CfA and PCM, respectively. The corresponding radius values (SeDeM diagram method) are 0.55 and 1.31 for both drugs, respectively, indicating the poor powder flow characteristics. However, calcium carbonate granules showed angle of repose value of 22.25 and 5.55 as the radius.

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. The radius values of flowability are 1.16 and 2 for CfA and PCM, respectively, depicting poor flow dynamics. The increase in cohesion plays a dominant role in flow dynamics as it directly impacts the bulk flowability of solid material. Increased cohesiveness can cause jamming of the flow of granular material, even under conditions where the cohesionless material flows. Flowability value and radius value for calcium carbonate granules was found to be 8.48 and 5.76, respectively.

The influence of sorbed moisture and hygroscopicity on powder flow and compaction is well established. 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. Percent LOD values for granules of CfA and PCM are 0.76, 0.43 and 1.82 and the radius values are 4.93, 7.14 and 2.72, correspondingly. LOD radius value for PCM is below the acceptable limit of 5.0, indicating the effect of moisture on flow of powders. However, certain other powder characteristics including the morphology of the particles may vary the flow properties. Percent hygroscoopicity (%H) values are 0.073 (radius 9.96) and 0.63 (radius 9.68) for CfA and PCM, respectively, and point towards the non-hygroscopic behavior. High hygroscopicity is undesirable for many reasons including handling problems, requirement of special storage conditions, and chemical and physical stability problems.

Particle size plays an extremely important role in the homogeneity of powder blends. The experimental values and corresponding radius values of %Pf (particles < 50 mm) and Iθ (homogeneity index) for both drugs are reported in Tables 2 and 3. The results implied that %Pf is showing promising direct compression suitability owing to high radius values. However, a considerably low radius values of Iθ are an object of concern. To obtain constant powder flow, the particle size should be carefully controlled. Flow properties of powders constituted of larger particles are less sensitive to variations in external stress such as experienced during scale up activities. Moreover, a considerable fraction of fine particles (size < 50 mm) is vital for direct compression applicability of the powders.

CONCLUSION

The values of Parametric index (IP), Parametric profile index (IPP) and Good compression index (GCI) are clearly indicative of poor direct compression suitability of both CfA and PCM. It is recommended that the selected drugs are required to be blended with suitable excipients so that the radius values, as per SeDeM diagram method, of the powder characteristic parameters will become > 5.0 making GCI acceptable. Thence, suitable compositional blend of single and/or multiple directly compressible ingredients with the selected API could be studied for direct compression suitability using SeDeM diagram method. In line of these observations SeDeM diagram method could be seen as a useful preformulation tool for galenic characterization of API and excipients with respect to their suitability for direct compression.

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