

Research Article

Preformulation Studies for Direct Compression Suitability of Polyethylene Oxide in Development of Solid Oral Dosage Form: A Graphical Representation Using SeDeM Diagram

*Sadhana Shah¹, Rahul Chate¹, Amol Dube¹, Imran Tadwee²

¹Government college of pharmacy opp. Government polytechnic osmanpura, Aurangabad-43100 (MH) India.
²Y.B Chavan College of Pharmacy Rouza Baugh, Aurangabad 431001

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*Corresponding author:
Dr. Sadhana Shahi
Government college of pharmacy
opp. Government polytechnic
usmanpura, Aurangabad-43100
(MH) India.
Email: sadhanashahi@yahoo.com

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Abstract

The main objective of the present work was to study the effect of application of SeDeM tool & to establish the data of excipient Polyethylene oxide (PEO) which will enables researchers or formulator to use the established data and statistics in their preformulation studies while developing formulation highlight the characteristics of PEO in terms of good flow properties which can be of a highest advantage in direct compression suitability of an excipient. These studies can be employed as a pre active step in the preformulation studies in design of pharmaceutical dosage form. In This study PEO as an inactive ingredient subjected for SeDeM studies, 12 Test were performed & the values obtained are subjected for conversion in to the factors to obtained radius value. Technical 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 PEO. Good compression index indicating good direct compression characteristics of the selected excipient Hence PEO is highly recommended excipient to be used in the formulation having poor flow API using direct compression method

Keywords: Polyethylene Oxide, SeDeM, Preformulation Studies, Galanic Method, Direct Compression, Powder flow

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Introduction

Polyethylene oxide is a polyether compound with many applications from industrial manufacturing to medicine. PEO is also known as polyoxyethylene, depending on its molecular weight. PEO water-soluble polymers are offered under the POLYOX™ brand name. They provide binding, thickening, lubricity, water retention, and film formation benefits to deliver excellent performance in a variety of applications in pharmaceuticals. They're also thermoplastic materials that are readily calendared, extruded, injection molded, or cast, to provide even greater formulation and processing flexibility¹. The good flow property of this material is having greatest advantage for use and application of PEO in above stated processes. Structure of PEO: $(-O-CH_2-CH_2-)_n OH$.

The end groups in PEO are known to be hydroxyl groups only in the case of the lower molecular weight species. Unlike most polymer systems, PEO is commercially available in an extraordinarily wide range of molecular weights from ethylene glycol, diethylene glycol, and so on up to polymers that have molecular weights many times greater than a million. The lower molecular weight members of the series with η up to about 150 are generally known as polyethylene glycols while the higher members are known as poly(ethylene oxide), polyoxyethylene, or polyoxirane. In this book, the term polyethylene oxide will be taken to include polymers of all molecular weights unless only the lower members are being discussed, in which case the term polyethylene glycol will be used. The higher and lower molecular weight members of the PEO series differ sufficiently in properties as to form two classes. The lower members range from relatively viscous fluids to wax-like solids while the higher members are true thermoplastics capable of being formed into tough, molded shapes. The property differences of these two classes are due principally to large differences in molecular weight and the relatively greater importance, therefore, of end-groups in the low molecular weight class. The extreme water solubility of PEOs of special interest in the light of the insolubility in water of polymers with such closely related structures as poly(methylene oxide), polyacetaldehyde, higher molecular weight (greater than about 1000) poly(propylene oxide), and poly(trimethylene oxide).²

Polymers of ethylene oxide are used in a wide variety of applications generally falling into two classifications depending on polymer molecular weight. The liquid and waxy polymers with molecular weights below about 6-8,000 have been commercially available since the 1930's and are widely used in formulating pharmaceuticals, cosmetics, sizings, and humectants. The high polymers with molecular weights of 100,000 and more are relatively new products having been introduced commercially in the 1960s. Applications depend on the unique solubility and rheology of these products and their thermoplastic character² PEO has very good advantage in novel drug delivery system. As it is non-ionic in nature, there is no any interaction with other excipients. PEO is a biocompatible eroding

polymer available in a number of molecular weights, which is receiving growing attention as sustained-release bioadhesive platform due to its safety, ease of processing (direct compression is feasible) and possibility to control drug release³

SeDeM Method

SeDeM Method is used in the preformulation studies which emphasis always on the physical properties of drug substances related to its suitability in the direct compression process. While in this article we are highlighting advantage of available excipient with good physical properties for its application or usage in the formulation with its statistics obtained after performing 12 test of SeDeM method, which is reliable method for preformulation studies and as a quality control tool for studying batch-to-batch reproducibility of API & Excipients. Furthermore, it establishes 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 which is having poor flow⁴ 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 (tn), 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^{5,6,7}. The details 12 tests of SeDeM and their units, equations factors are explained in Table 1

Materials & Method

PEO WSR1105 grade excipient is obtained from Wockhardt Pharmaceuticals Aurangabad as a gift sample pharmacopoeia methodologies are used to calculate parameters of SeDeM as well as a common strategy used in pharmaceutical technology development is applied for constructing the SeDeM Diagram. The methods used for each test are described below⁶

1) 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.

2) 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 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

$$Ie = Dc \cdot n \cdot Da / Dc \cdot X \cdot Da$$

4) Carr index (IC %)

It was computed from Da and Dc using the following equation

$$IC = (Dc \cdot n \cdot Da / Dc) \cdot 100$$

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 and the 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:

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

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 Pharmacopoeia⁸. Excipient PEO was dried in a convection oven at $105^{\circ}\text{C} \pm 2^{\circ}\text{C}$ 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 $76\% \pm 2\%$ and a temperature of $22^{\circ}\text{C} \pm 2^{\circ}\text{C}$ 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 (I0)

The method for determination of I0 was based on General method 2.9.12 of European Pharmacopoeia⁹ 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:

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

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.

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: Parameters & Factors for radius calculation used in SeDeM Diagram Method

Parameter (Symbol)	Unit	Equation	Limit Value	Radius	Factor Applied
Bulk Density (Da)	gm/ml	Da= P/Va	0-1	0-10	10v
Tapped Density (Dc)	gm/ml	Dc= P/Vc	0-1	0-10	10v
Interparticle porosity (Ie)	-	Ie= DC-Da/Dc x Da	0-1.2	0-10	10v/1.2
Carr index (Icd)	%	IC = (Dc-Da/Dc)	0-50	0-10	10-(v/5)
Cohesion index (IC)	N	Experimental	0-200	0-10	v/20
Hausner Ration (IH)	-	IH=Dc/Da	3-0	0-10	10-(10v/3)
Angle of repose (α)	-	A =tan ⁻¹ h/r	50-0	0-10	10-(v/5)
Flowability (t ⁿ)	S	Experimental	20-0	0-10	10-(v/2)
Loss on Drying (% LOD)	%	Experimental	10-0	0-10	10-v
Hygroscopicity (%H)	%	Experimental	20-0	0-10	10-(v/2)
Particles <50 m (%Pf)	%	Experimental	50-0	0-10	10-(v/5)
Homogeneity index (Iθ)	-	Eq. (1)	0-0.02	0-10	500v

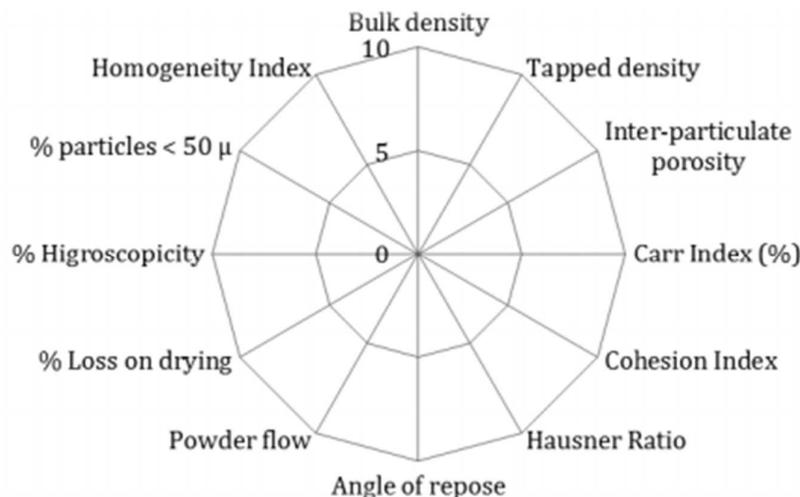


Fig. 1: 12 Tests of SeDeM Diagram

Result & Discussion

The experiments were performed in duplicate 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 (V_1 , V_2), the mean of experimental values (V) and respective radius values (R_1 , R_2), the mean of radius values (R) of different flow parameters were for PEO shown in the table 2. Also the type of flow can be compare with the limits given in USP shown in table 3 scale of flowability. These calculated radius values were graphically expressed on a regular circle graph (histogram) 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 reverse is expected. The void age fractions of tapped and loosely packed powder beds have been known to be related semi empirically to the size distribution, shape, and density of the constituent particles^{7, 10}. 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 PEO are 0.384 and 0.55 respectively.

Interparticle porosity was found to be 1.17 for PEO with 9.75 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 non-free flowing powders. Cohesion index reflects the stability of the rapid particular rearrangements of powder. Cohesion index values of PEO found to be 93.6 with radius value 4.68 indicating good compaction suitability of the granules. 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. Experimental value of Carr index is 30.9 & the calculated radius values of Carr index is 6.18 for PEO SeDeM results of Hausner ratio values 1.44 eith radius of 7.8. SEDEM results of Hausner ratio is acceptable. 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 21 and the corresponding radius values (SeDeM diagram method) is 5.8 indicating the excellent powder flow characteristics (table 3). 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 is 7.5 depicting good 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 cohesion less material flows⁷. 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 is 0.5% w/w & the radius values is 9.5. LOD radius value is above the acceptable limit of 5.0. However, certain other powder characteristics including the morphology of the particles may vary the flow properties. Percent hygroscopicity (%H) values is 0.5 (radius 9.75) and pointing 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 %Pf (particles < 50 mm)

and I θ (homogeneity index) reported in Tables 2 The results implied that %Pf is showing promising direct compression suitability owing to high radius values. 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 μ m) is vital for direct compression applicability of the powders. The values of Parametric index (IP), Parametric profile index (IPP) and Good compression index (GCI) are 0.75, 6.77 and 6.44 respectively which shows high suitability of this excipient for direct compression.

Table 2: Experimental & Radius values

Sr. No	Parameter (Symbol)	Acceptable value Limit	Value obtained (V)	Acceptable Radius Limit	Corresponding Radius (R)
1	Bulk Density (Da)	0-1	0.384	0-10	3.84
2	Tapped Density (Dc)	0-1	0.550	0-10	5.50
3	Interparticle porosity (Ie)	0-1.2	1.17	0-10	9.75
4	Carr index (Icd)	0-50	30.9	0-10	6.18
5	Cohesion index (IC)	0-200	93.6	0-10	4.68
6	Hausner Ration (IH)	3-0	1.44	0-10	7.8
7	Angle of repose (α)	50-0	21	0-10	5.8
8	Flowability (t^{θ})	20-0	5	0-10	7.5
9	Loss on Drying (% LOD)	10-0	0.5	0-10	9.5
10	Hygroscopicity (%H)	20-0	0.5	0-10	9.75
11	Particles <50 m (%Pf)	50-0	18	0-10	6.4
12	Homogeneity index (I θ)	0-0.02	0.09	0-10	4.5

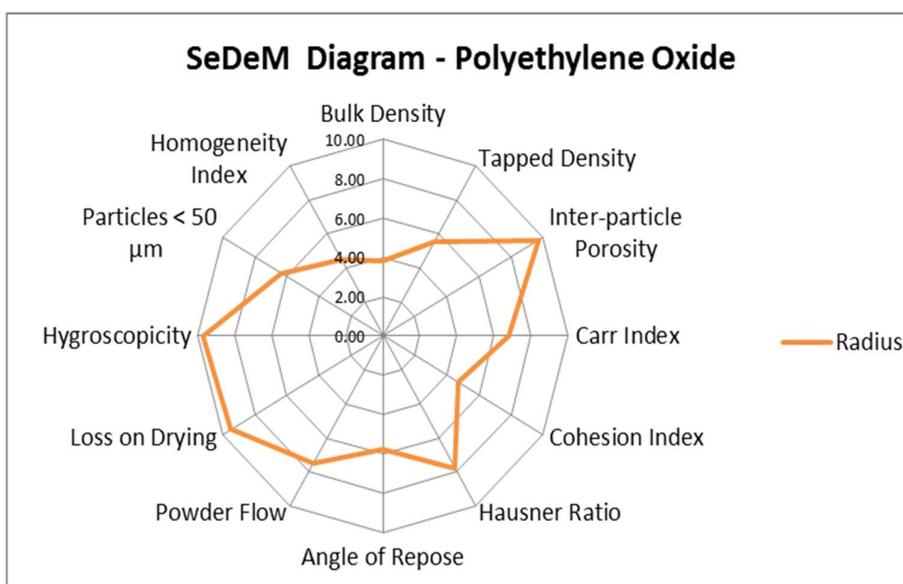


Fig 2: SeDeM Diagram of PEO

Table 3: Scale of flowability

Flow Characters	Carr Index	Hausner Ration	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

Conclusion

SeDeM parameters studied on PEO, study results indicates PEO is suitable candidate for direct compression. The values of Parametric index (IP), Parametric profile index (IPP) and Good compression index (GCI) shows that PEO can be a choice of excipient and can be incorporated with API having poor flow. Values applied in SeDeM diagram which reveals that 9 of 12 parameters having radius equals to or more than 5 which indicates that PEO is choice of excipient can mask poor flow property of drug substances. Based on the result obtained PEO is recommended to be used in formulation. 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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Conflict of Interest

All Authors declares no conflict of interests

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