# SUPPLEMENTAL DATA

*Physical characterization of raw materials using the SeDeM diagram*

The SeDeM expert system is helpful in preformulation studies. And the SeDeM diagram was performed in this paper to evaluate the batch-to-batch and source-to-source variations of PNS extracts. Originally, the SeDeM diagram was made up of twelve parameters which were divided into five groups, i.e. dimension, compressibility, flowability/particle flow, lubricity/stability, and lubricity/dosage, and the corresponding reliability factor of the method was calculated as the ratio of polygon area and circle area. However, in this study, another two properties, i.e. the specific surface area and the true density, are added to improve the reliability (reliability factor=0.967) of the method with little detriment of its simplicity and rapidity (as shown in Table 1).

Bulk density and tapped density were obtained on the basis of the British Pharmacopoeia 8.0. Bulk density ($D_a$) was firstly determined by measuring the volume of per 100 g of samples with a 250 mL cylinder. Then tapped density ($D_c$) was obtained after 1250 strokes using a powder density tester (HY-100, Dandong Hylology Co. Ltd, P. R. China) with above samples.

Inter-particle porosity (*Ie*), Hausner ratio (*IH*) and Carr index (*IC*) were calculated by the following equations:

$$Ie = \frac{D_c - D_a}{D_a \times D_c}$$

$$IH = \frac{D_c}{D_a}$$

$$IC = \frac{D_c - D_a}{D_c} \times 100$$

The specific surface area (*SSA*) and the true density ($D_t$) of PNS extracts were measured by applying 3H-2000PS1 specific surface & pore size analysis instrument

(Beishide Instrument Technology Co., Ltd, Beijing, P.R.China). Samples were weighed and were then poured into the sample tubes with filler rods. Before measurement， samples were degassed at 120 ℃ for 2.5 h to keep the surface of the extracts clean enough. Partial pressure points for nitrogen at 77 K were set between 0.05 and 0.30 bar, spilt equally in 6 points and the equilibration time was 10 s. The *SSA* data for PNS extracts were determined based on the Brunauer-Emmett-Teller (BET) adsorption isotherm analysis. Before measuring the true density, PNS extracts were kept in the blast oven for 24 hours to eliminate the influence of moisture. The volume ($V_1$) of the empty sample tube was tested until the error percentage was under 0.05% with pure helium. Samples were then poured into the sample tube weighed as *m* and were purged with helium again to test the volume ($V_2$) of the sample tube with extracts. The true density was calculated as follows:

$$D_t = \frac{m}{V_1 - V_2}$$

Cohesion index (*Icd*) was determined by compressing the powder in an eccentric press. And the value of *Icd* was expressed as the hardness (N) of the obtained tablet. If the raw powder could not be compressed, 3.5% of the mixture need to be added: talc 2.36%, Aerosil 0.14% and magnesium stearate 1.00%.

The angle of repose ($\alpha$) was quantified with the flow ability tester (BEP2, Copley Inc., England) according to the British Pharmacopoeia 8.0. About 100 grams of powders flowed through the 10 mm nozzle slowly until a stable heap was formed. The cone base diameter is 100 mm. The height of the powder cone was recorded to calculate the inverse tangent to obtain the angle of repose as follows:

$$\alpha = \arctan(\frac{2 \times h_c}{d_c})$$

Where $\alpha$ is the angle of repose; $h_c$ is the height of the cone; and $d_c$ is the diameter of the cone base. Flowability (*t*) is expressed in seconds and tenths of per 100 grams of sample, with the mean value of three determinations being taken.

The moisture content (*MC*) was measured by the rapid infrared moisture analyzer

(MA 35, Sartorius, Germany). Approximately 1g of the sample was distributed evenly over the testing disc at 105 ℃ and the result was noted until the weight of samples kept constant. Hygroscopicity (%*H*) was served as the sample weight increase after being kept in a drier at relative humidity of 75% and at environmental temperature of 25 ℃ for 24 h.

Percentage of particles measuring <50μm (*%Pf*): It was measured by the laser diffraction and the value is the percentage of particles that is less than 0.05mm.

Homogeneity index (*Iθ*): This was determined by the laser diffraction and defined particle interval points were 0.355 mm, 0.212 mm, 0.100 mm and 0.050 mm. The percentage of product retained in each range was automatically calculated. The following equation is applied to the data collected.

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

Where $I\theta$ is relative homogeneity index; $F_m$ is percentage of particles in the majority range; $F_{m-1}$ is percentage of particles in the range immediately below the majority range; $F_{m+1}$ is percentage of particles in the range immediately above the majority range; $n$ is order number of the fraction studied under a series, with respect to the majority fraction, $d_m$, means diameter of the particles in the majority fraction; $d_{m-1}$ means diameter of the particles in the fraction of the range immediately below the majority range; and $d_{m+1}$ means diameter of the particles in the fraction of the range immediately above the majority range.

The values obtained are converted to the same scale from 0 to 10 based on the SeDeM method (Table 1). The SeDeM diagrams were therefore formed by the normalized radius values, indicating the characteristics of the PNS extracts. The diagram is made up of 14 parameters, which would form an irregular 14-sided polygon.

Table 1. Parameters and tests used by the SeDeM method

| Incidence | Parameter | Symbol | Unit | Equation | Limit value | Factor applied |
|---|---|---|---|---|---|---|
| Dimension | Bulk density | $D_a$ | $g \cdot mL^{-1}$ | $D_a = P/V_a$ | 0-1 | 10*v* |
| | Tapped density | $D_c$ | $g \cdot mL^{-1}$ | $D_c = P/V_c$ | 0-1 | 10*v* |
| | True density | $D_t$ | $g \cdot mL^{-1}$ | Experimental | 0-2 | 5*v* |
| Compressibility | Inter-particle porosity | *Ie* | - | $Ie=D_c-D_a/D_c*D_a$ | 0-1.2 | 10*v*/1.2 |
| | Carr Index | *IC* | % | $IC=(D_c-D_a)/D_c*100$ | 0-50 | *v*/5 |
| | Cohesion index | *Icd* | N | Experimental | 0-200 | *v*/20 |
| | Specific surface area | *SSA* | $g \cdot m^{-2}$ | Experimental | 0-1 | 10*v* |
| Flowability/ Powder flow | Hausner ratio | *IH* | - | $IH=D_c/D_a$ | 3-1 | 10-(10*v*/3) |
| | Angle of repose | $\alpha$ | ° | $tg\alpha=h/r$ | 50-0 | 10-(*v*/5) |
| | Powder flow | *t* | s | Experimental | 20-0 | 10-(*v*/2) |
| Lubricity/stability | Moisture content | *MC* | % | Experimental | 10-0 | 10-*v* |
| | Hygroscopicity | *%H* | % | Experimental | 20-0 | 10-(*v*/5) |
| Lubricity/dosage | Particles<50 μm | *%Pf* | % | Experimental | 50-0 | 10-(*v*/2) |
| | Homogeneity index | *Iθ* | - | Iθ=Fm/100+ΔFmn | $0-2\times10^{-2}$ | 500*v* |