Evaluation of Raw Material Characteristics to improve Formulation design and Process output using TA.XT+ Powder flow analyser

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Overall scope of the project

- Characterize critical physical properties of raw materials
- Use this information to get process insight to better understand and control vitamins unit operations

⇒This information is necessary to achieve real time release

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Development Goals

- Select methods that can give relevant information on the kind of particulate systems Wyeth is processing
- Demonstrate how the selected methods work for a representative set of samples

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Powder flow analyser

- The TA.XT is equiped with the Powder Flow Analyser
- The appropriate amount of powder is placed in the normalized beaker
- Different tests can be performed with the especially designed blade

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Measurement of powder characteristics

Tests
- Cohesion / Compaction Index
- Powder Flow Stability Dependence (PFSD) Index
- Caking Index

Raw materials*
- Calcium Pantothenate
- Stearic Acid
- Potassium Chloride
- Vitamin A
- Beta Carotene
- Xylitab
- Calcium Phosphate
- Magnesium Stearate

*Selected to provide a range of behaviours, based on qualitative observations made by production staff during processing

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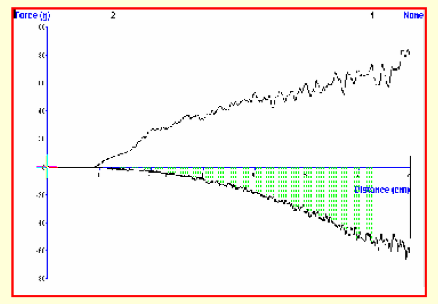
Cohesion / Compaction Index

- 2 conditioning cycles
- 3 measurements consisting in :
  - Compacting slightly the powder
  - Removing the blade from the powder and measuring the force
- The Cohesion Index is obtained when dividing the "negative" area under the curve by the weight

- Data treatment and interpretation



⇒The lower the value, the less cohesive the powder is

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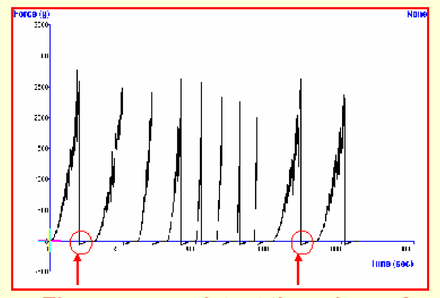
Flowability Index

- 2 conditioning cycles
- 5 consecutive compaction cycle at 4 different speed
  - 1 at 10 mm/sec
  - 1 at 20 mm/sec
  - 1 at 50 mm/sec
  - 1 at 100 mm/sec
  - 1 at 10 mm/sec
- The Flowability index is obtained when dividing the area under the curve by the weight

- Data treatment and interpretation



- The more consistent the values of Flowability index are, the less affected by the speed and the handling the powder is

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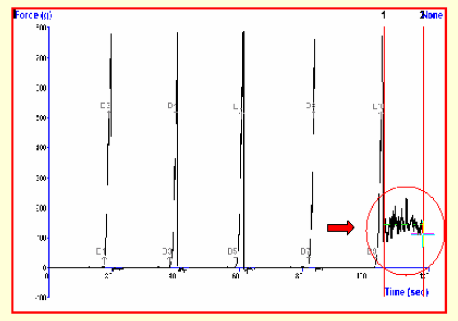
Caking Index

- 2 conditioning cycles
- 5 consecutive compaction
- 1 cycle of "cake cutting" using a different angle of penetration
- The Caking Index (CI) is obtained when measuring the force applied on the cake and dividing this force by the weight

- Data treatment and interpretation



- The highest the value is, the more the powder is prone to cake

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Typical results

Materials	Lot #	Value $_{PFSD}$	Value $_{Caking}$	Value $_{Cohesion}$
Calcium Pantothenate	1	1.06	51.42	9.07
Calcium Pantothenate	2	1.15	49.37	9.33
Calcium Pantothenate	3	1	51.078	9.74
Stearic acid	1	1.02	89.989	18.03
Stearic acid	2	1.01	106.28	19.06
Stearic acid	3	0.98	139.024	22.45
Vitamin A	1	1.01	18.065	10.96
Vitamin A	2	1.04	157.95	9.33
Vitamin A	3	1.02	19.621	10.26
Potassium chloride	1	0.93	49.22	10.83
Potassium chloride	2	0.56	20.84	9.6
Potassium chloride	3	0.85	103.489	10.33
Bêta Carotène	1	0.93	36.929	10.41
Bêta Carotène	2	1.16	32.41	10.19
Bêta Carotène	3	1.07	50.774	9.51

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Statistical method of analysis

Statistical method applied on the results

- Discriminate outliers and identify dubious data points
- Compare individual points with the standard deviation
- Predetermined values for eliminating out-of-spec data
- Discriminating method for comparing a single value to a mean

➡ Chauvenet's criterion =

$$\frac{Abs(mean \cdot value - measured \cdot value)}{StdDEV}$$

Number of readings n	Ratio of maximum acceptance deviation to standard deviation
3	1.38
4	1.54
5	1.65
6	1.73
7	1.8
10	1.96
15	2.13
25	2.33
50	2.57
100	2.81
300	3.14
500	3.29
1000	3.48

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Conclusions

- Three physical characterization methods were selected
  - Powder Flow Stability Dependence (PFSD) Index
  - Caking Index
  - Cohesion / Compaction Index
- First results give insight on our raw material physical characteristics
- Physical characterization show differences in the raw materials tested by the mean of the different indexes numbers
- More testing is needed to understand better the behaviour of the raw materials and the real meaning of the indexes

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Next Steps

- Conduct testing on a more statistically representative set of samples
- Conduct development tests at commercial scale for more materials
- Present first results from commercial development

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Next Steps

Selected tests
- Cohesion / Compaction Index
- Powder Flow Stability Dependence (PFSD) Index
- Caking Index

Selected raw materials*
- Calcium phosphate Dibasic USP/EP dihydrate Unmill
- Magnesium Oxide USP heavy
- Microcrystalline Cellulose NF/EP
- Vitamin E USP Acetate dl dry 50%
- Crospovidone NF
- Ferrous Fumarate USP
- Niacinamide USP/EP 100% DC
- Biotin 1% MFR STD
- Beta-Carotene 20% MFR STD

*Selected according to their usage frequency in production

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Next steps

1. Fast track development
   - Fine tuned methods
   - Quickly create a data bank
2. Long term study
   - Create a complete databank mapping the behaviour of our critical materials
   - Determine how to identify and manage variability in raw materials

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50 ans L'audace porte fruit

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