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In-line Blend Homogeneity Evaluation with PAT Tools

Abstract

Context/Rationale

Process control is gaining importance in the pharmaceutical manufacturing industry due to a strong need to monitor and control the critical process parameters influencing the critical quality attributes of the product and to understand better unit operations involving particulate systems handling.

Objectives

This project was aimed at the in-line evaluation of blend homogeneity with the use of a Process Analytical Technology (PAT) applied on lab scale and full scale production lots of pharmaceutical blender unit operations.

Methodology

The study was aimed at answering the need of a typical production plant by identifying the Pros and Cons of different analytical tools and homogeneity determination methods and was applied to lab scale and production scale V-Blenders and Bin-Blenders. The formulation used was a Wyeth multi-vitamin formulation of 16 ingredients with concentrations ranging from less than 1 wt% to more than 40 wt%.

Conclusions

The results provide a Process Analytical Technologies (PAT) tool permitting to (a) evaluate in-line blends homogeneity and consequently mixing end-point and (b) to identify the process control strategy that is most appropriate for the plant in the targeted formulation.

Introduction

- cGMP states in CFR Parts 211.110a(3):

  "To assure batch uniformity and integrity of drug products , written procedures shall be established… Such control procedures shall include…: Adequacy of mixing to assure uniformity and homogeneity."

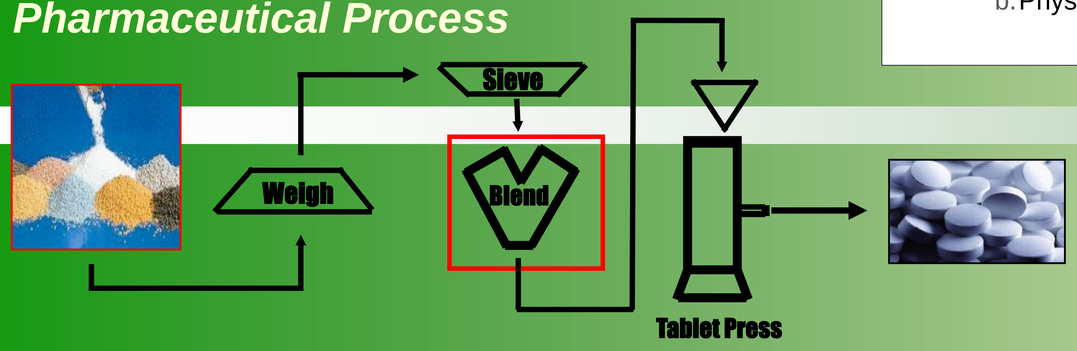
- The case of the FDA vs. Barr Laboratories (1993)
- The Blend Uniformity Working Group (BUWG)'s recommendations for blend sampling. (2002)

  Validation batch → 10 sampling locations in blender + in process analysis

  Routine batch → In process analysis

- To this day, very few manufacturers are fully in compliance with BUWG's recommendations
- Incidentally, a low concentration active or a complex formulation may well segregate while going through the many unit process steps.
- Blenders are the first production step where powder homogeneity must be evaluated.

Typical direct compression Pharmaceutical Process



Objectives

- Develop a tool used to determine mixing end-point
- Develop a uniformity and/or homogeneity assessment method

Opportunities

- ✓ Process Insight / Quality by Design (QbD)
- ✓ Part of Real-time release initiative
- ✓ Reduced testing
- ✓ Time to market reduction for new formula

Technology Considered

➢ **UV Spectroscopy**
Pros: Fast scan time
Cons: not adapted for powder analysis

➢ **Raman Spectroscopy**
Pros: High Specificity, minerals and organics
Cons: long scan time, laser safety, powder sample integrity

➢ **LIF Spectroscopy**
Pros: Compact, Can analyze traces
Cons: Univariate, product-dependent specificity

➢ **Thermal Effusivity measurements**
Pros: Robust, simple
Cons: Long scan time, Uni-variate, low specificity

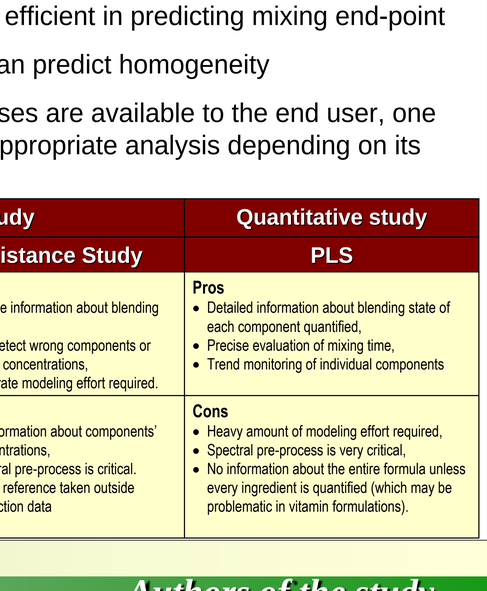
Technology Selected

NIR spectroscopy

- Near Infrared is the region 800-2500nm in the electromagnetic spectrum (1350 to 1800 scanned)
- NIR spectrum = molecular fingerprint
- Fast measurements
- Non-Destructive & non-invasive
- Sensible to organic molecules
- Spectra vary depending on:
  a. Chemical properties
  b. Physical properties

Methodology

1. Review of literature for types of Multi-variate Data Analysis
2. Small-scale application of Data Analysis with Lab reference comparison
3. Scale-up on production powder-mixing unit operation:
   i. 125 ft³ V-Blender
   ii. 1400L Bin-Blender



Results

Analysis of spectral variance
- ➢ No reference required
- ➢ Quick application to every formula

$$\delta^2 = \frac{\sum_{i=1}^{N} \left| A_{t_1}^{\ 2} - A_{t_0}^{\ 2} \right|}{N}$$

Analysis of distance
- ➢ Homogeneous reference required
- ➢ Qualitative information about ingredients and concentrations

$$T_i^2 = \sum_{a=1}^{A} \frac{t_{i,a}^2 - \bar{t}_a}{s_{t,a}^2}$$

Quantitative analysis
- ➢ Heavy MVDA modeling required
- ➢ Precise information about the quantified ingredients

Data Pre-Process⇒ *PCA*⇒ *PLS*⇒ *Quantitative_Model*

Conclusions

- ☑ NIR spectroscopy is efficient in predicting mixing end-point
- ☑ NIR Spectroscopy can predict homogeneity
- ☑ Many types of analyses are available to the end user, one should choose the appropriate analysis depending on its needs

Qualitative study		Quantitative study
Variance study	**Distance Study**	**PLS**
Pros • Quick implementation for every formula, • Diminish error due to reference selection, • Spectral pre-process less critical.	**Pros** • Precise information about blending state, • Can detect wrong components or wrong concentrations, • Moderate modeling effort required.	**Pros** • Detailed information about blending state of each component quantified, • Precise evaluation of mixing time, • Trend monitoring of individual components
Cons • No information about components' concentrations, • No information about types of components. • Can slightly underestimate blending time.	**Cons** • No information about components' concentrations, • Spectral pre-process is critical. • Bias if reference taken outside production data	**Cons** • Heavy amount of modeling effort required, • Spectral pre-process is very critical, • No information about the entire formula unless every ingredient is quantified (which may be problematic in vitamin formulations).

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