Calibration of multivariate predictive models: 1) application of Raman spectroscopy to tablet content assay and 2) study of factors and parameters influencing performances of MVDA-based PAT methods.

Challenges in pharma industry

- Higher raw material and operating costs;
- Higher need in finished product quality testing;
- Need to lower retail price.

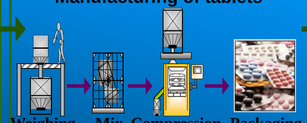
One of the solutions

☑ Implantation of Process Analytical Technologies (PAT)
- ◎ For process monitoring;
- ◎ For quality testing.

PAT application examples

Reception & testing of raw materials → **Manufacturing of tablets** → **Product quality testing**

Conformity testing (several days)

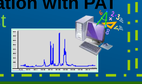


Weighing — Mix — Compression — Packaging

Appearance and chemical tests (weigh, ICP, HPLC…)

☒ Costly ☒ Laborious ☒ Long

Identification with PAT
☑ Low cost
☑ Fast
☑ «Easy»



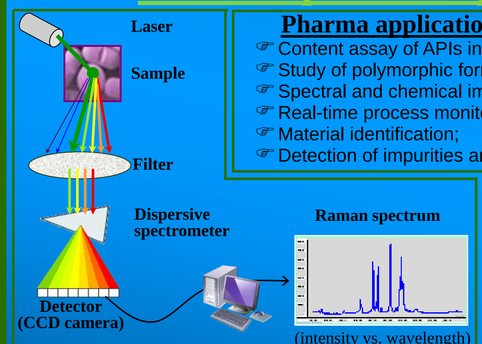
On-line monitoring of powder mixing and flowing
☑ Fast ☑ Lower risks
☑ Allow better process insight

Quality testing with PAT

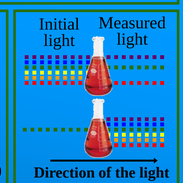
☑ Fast
☑ Safe

Section 1
Context and theory

Raman spectroscopy



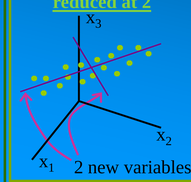
Pharma application examples
- ☞ Content assay of APIs in finished products;
- ☞ Study of polymorphic forms;
- ☞ Spectral and chemical imaging;
- ☞ Real-time process monitoring;
- ☞ Material identification;
- ☞ Detection of impurities and contaminants.



Multivariate data analysis

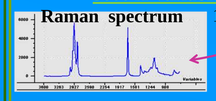
Data reduction

3 X-variables reduced at 2

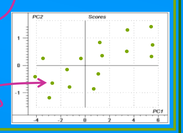


MVDA:
- ☞ Projects x-data in a space with less dimensions;
- ☞ Finds latent variables hidden in the original data;
- ☞ Explains most of the original variance with a few meaningful variables;
- ☞ Allows to exclude the noise.

3000 X-variables reduced at 2



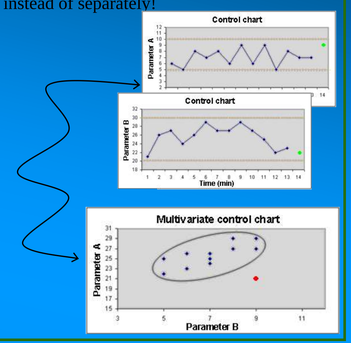
1 sample with 3000 Xs



Samples projected in the new 2-variable space

Structure revealing

Often, useful information can be discovered when the data at hand is considered as a whole instead of separately!



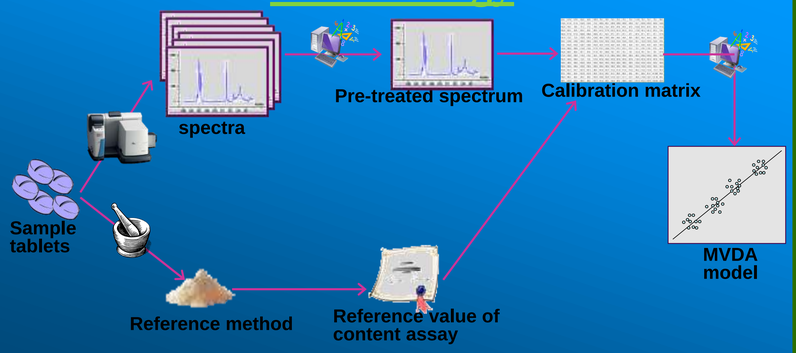
Objectives

◎ **To develop a Raman spectroscopic method to achieve one-minute content assay in pharmaceutical tablets, towards real-time release of finished product.**

Project plus-value

- ☑ **Increase test capacity within the batch;**
- ☑ **Increase process and product insight;**
- ☑ **Increase troubleshooting capacities;**
- ☑ **Decrease manufacturing and testing costs**
- ☑ **Lower burden of QC/QA laboratories;**
- ☑ **Lower use of dangerous solvents;**
- ☑ **Decrease overall product cycle time;**
- ☑ **Allow real-time release of product.**

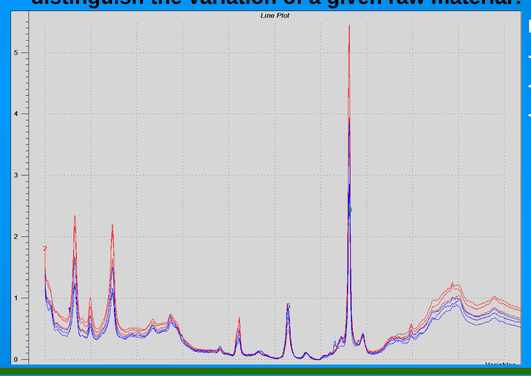
Methodology



Section 2:
Application project

Preliminary work

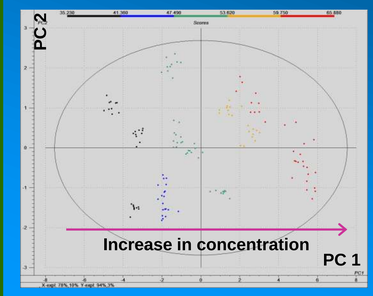
◎ **In a product containing 17 raw materials, is it possible to distinguish the variation of a given raw material?**

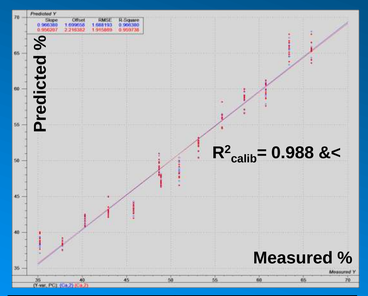


Monitorable:
- **4 minerals**
- **1 vitamin**
- **1 excipient**

Preliminary results

◎ **Is it possible to obtain a content assay that is as precise and as accurate as the reference method in the QC/QA lab?**





◎ **After the full development, it may be possible to replace part of or the totality of traditional content assay:**

☑ **No more wet chemistry!!**

Error (abs) (%):	mean	min	max
Mineral 1 (<5w%)	6.53	0.34	17.22
Mineral 2 (≈50w%)	2.43	0.15	8.33
Mineral 3 (<0.5w%)	10.30	0.32	36.90
Mineral 4 (<0.5w%)	29.26	2.22	50.59
Excipient 1 (≈1w%)	4.84	0.08	21.04

Possible future developments

- ◎ **Content assay in other tablet-form products;**
- ◎ **Raw material identification;**
- ◎ **Detection of impurities in raw materials;**
- ◎ **Content assay in powder premixes;**
- ◎ **Content assay in other product posologic forms.**

Why this project in the industry?

Before	After
◎ XXX days of testing;	◎ 10 minutes test;
◎ Several qualified chemists;	◎ 1 operator;
◎ Sample transfer to QA/QC lab.	◎ Test done in the compression room.

Context & problem

The development of a PAT method is a complex process that requires a lot of:
- Workforce:
  - ☞ project leader, consultants, help, client…);
- Time:
  - ☞ Known method: 1 year
  - ☞ New method: 2 years
- Resources;
  - ☞ Raw materials;
  - ☞ Small-scale equipment;

There are only a few guidelines regarding the best way to approach the development:
- Scientific papers:
  - ☞ Only a few.
- Past experience:
  - ☞ Is not based on sound scientific concepts.
- Trial and error;
  - ☞ Requires tremendous investments.

- **What influences the performances of a multivariate predictive model, and how?**
- **How can we optimize and quicken the development process?**

Section 3:
Research project

Objectives

◎ **Identify controllable factors and parameters that lengthen method development process and/or that are critical to the quality of the results and determine whether each factor has a significant influence on the method performance.**

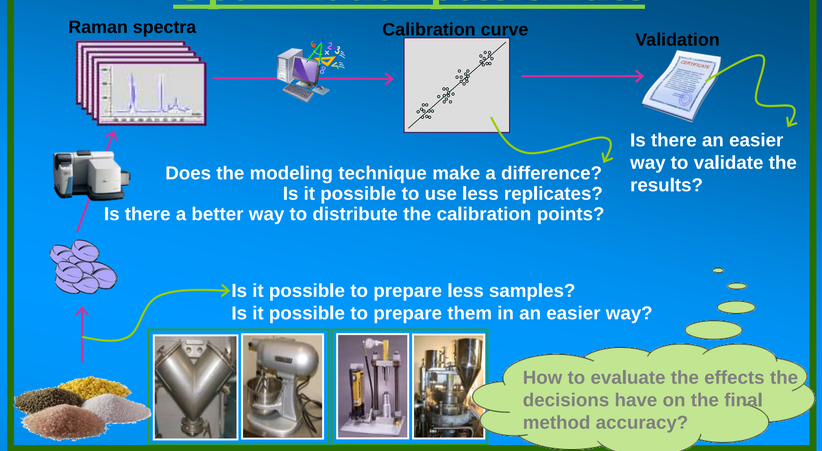
Project plus-value

- ☑ **Increase method development process insight and knowledge;**
- ☑ **Increase troubleshooting capacities;**
- ☑ **Increase confidence in future model capacities and reliability;**
- ☑ **Lower burden of development;**
- ☑ **Lower overall time and costs for method development;**
- ☑ **Allow applications on more complex product formulation.**

Expected completion date

- **Actual work and analysis:** September 2009
- **Redaction activities:** January 2010

Optimization possibilities



Poster prepared by Joanny Salvas

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Research project under the direction of Pr Nicolas Abatzoglou, department of chemical engineering & the supervision of Mr. Jean-Sébastien Simard.

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Chaire [illegible] sur les technologies d'analyse de procédés en génie pharmaceutique

ISPE Engineering Pharmaceutical Innovation