Innovation & Collaboration for Process Analytical Technology & Advanced Pharmaceutical Manufacturing

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EUROANALYSIS Barcelona 2025

PUERTO RICO | Science, Technology & Research Trust

REFERENCE: FY2014-15-#01

Preference will be given to projects that demonstrate:

- Projects to develop technologies and innovation within the strategic sectors being fostered by the State Government.
- Address a strong market need and have strong commercialization potential;
- Conducted collaboratively with industry as a proof of feasibility and early adoption of the resulting technology.
- Promote technology transfer from local universities to the private sector.
- Feasibility to result in the development of locally developed intellectual property, preferable through patent applications.

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- Begin with the end in mind. Everything is an idea first, before it happens.[1] It's a world of ideas.
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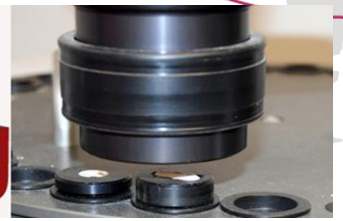
1. Covey, S. (1989). The seven habits of highly effective people. Simon & Schuster.
2. Morrison, E., Hutcheson, S., Nilsen, E., Fadden, J., & Franklin, N. (2019). Strategic doing: Ten skills for agile leadership. John Wiley & Sons.

Puerto Rico

- $53 billion in biopharma exports – largest in US. 161 km x 56 km.
- 35 pharma mfg sites including CMDO's, and 32 medical device sites, approx. 94,000 jobs.
- Exports pharm products to over 120 countries.

Poised for global transshipment

Strategic geographic location



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FULL PAPER

THE ANALYST

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Near-infrared libraries in the pharmaceutical industry: a solution for identity confirmation

M. Blanco* and M. A. Romero

Departament de Química, Unitat de Química Analítica, Facultat de Ciències, Universitat Autónoma de Barcelona E-08193. Bellaterra, Spain

Monitoring alcoholic fermentation by joint use of soft and hard modelling methods

Marcelo Blanco[a,*], Antonio C. Peinado[a], Jordi Mas[b]

Quality by Design Approach of a Pharmaceutical Gel Manufacturing Process, Part 1: Determination of the Design Space

JUAN G. ROSAS,[1] MARCEL BLANCO,[1] JOSEP M. GONZÁLEZ,[2] MANEL ALCALÁ[1]

API Determination by NIR Spectroscopy Across Pharmaceutical Production Process

M. Blanco,[1,3] M. Bautista,[1] and M. Alcalà[2]

On-Line Monitoring of A Granulation Process By NIR Spectroscopy

MANEL ALCALÀ,[1] MARCELO BLANCO,[1] MANEL BAUTISTA,[1] JOSEP M. GONZÁLEZ[2]

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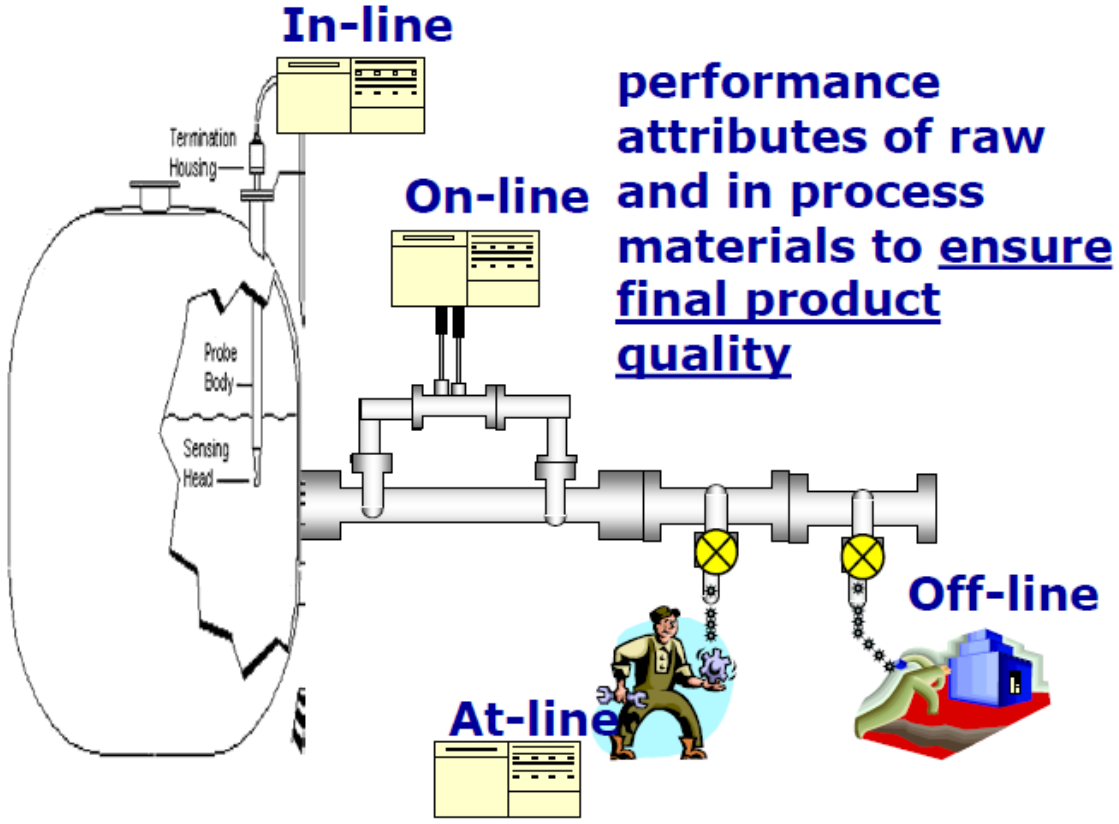
Innovation

- Requires inspiration and an open mind to new ways of thinking and moving beyond current established practices.[1]
- "Build products, services & experiences that break through". Design something better.[2]

1. Brown T. Change by Design: How Design Thinking Transforms Organizations and Inspires Innovation. First. Harper Business; 2009
2. https://www.ideo.com/offers, Accessed August 25, 2025.

Process Analytical Technology –Timely Measurements

Design, Analysis & Control of Mfg with measurements obtained during processing for critical quality and

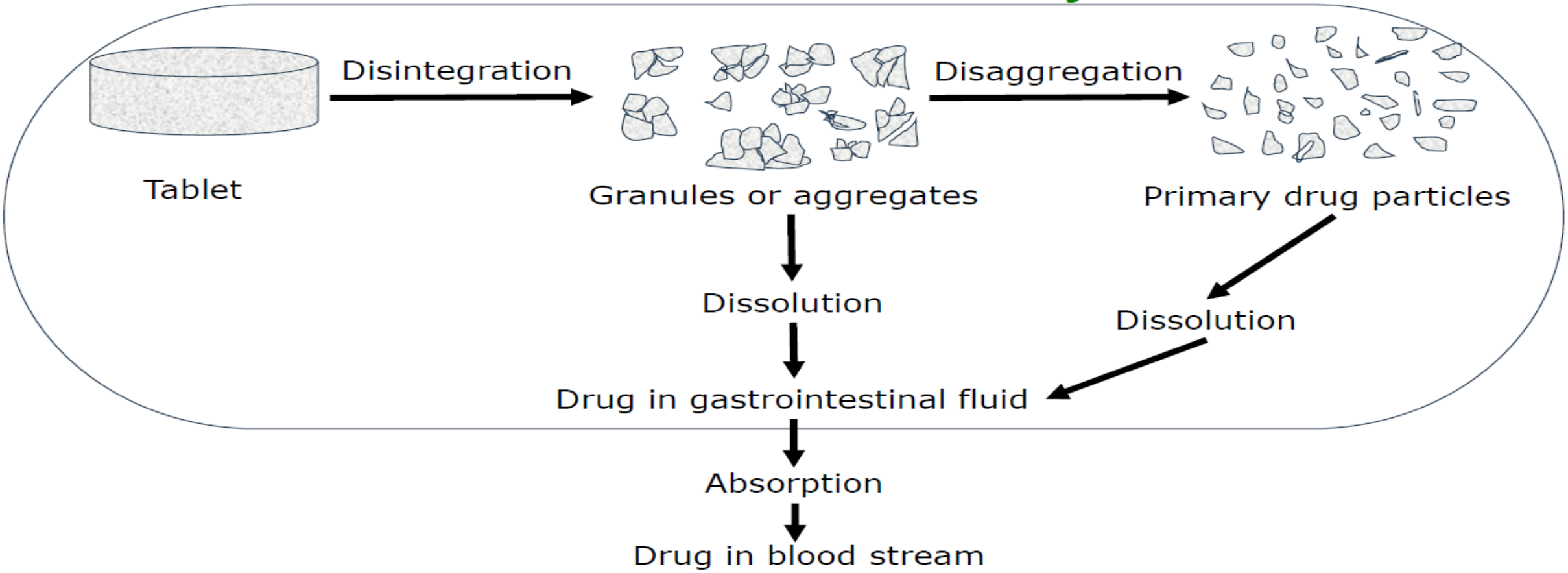


Scope: "The scientific, risk-based framework outlined in this guidance, Process Analytical Technology or PAT, is intended to support innovation and efficiency in pharmaceutical development, manufacturing, and quality assurance."

FDA Draft Guidance, 2004

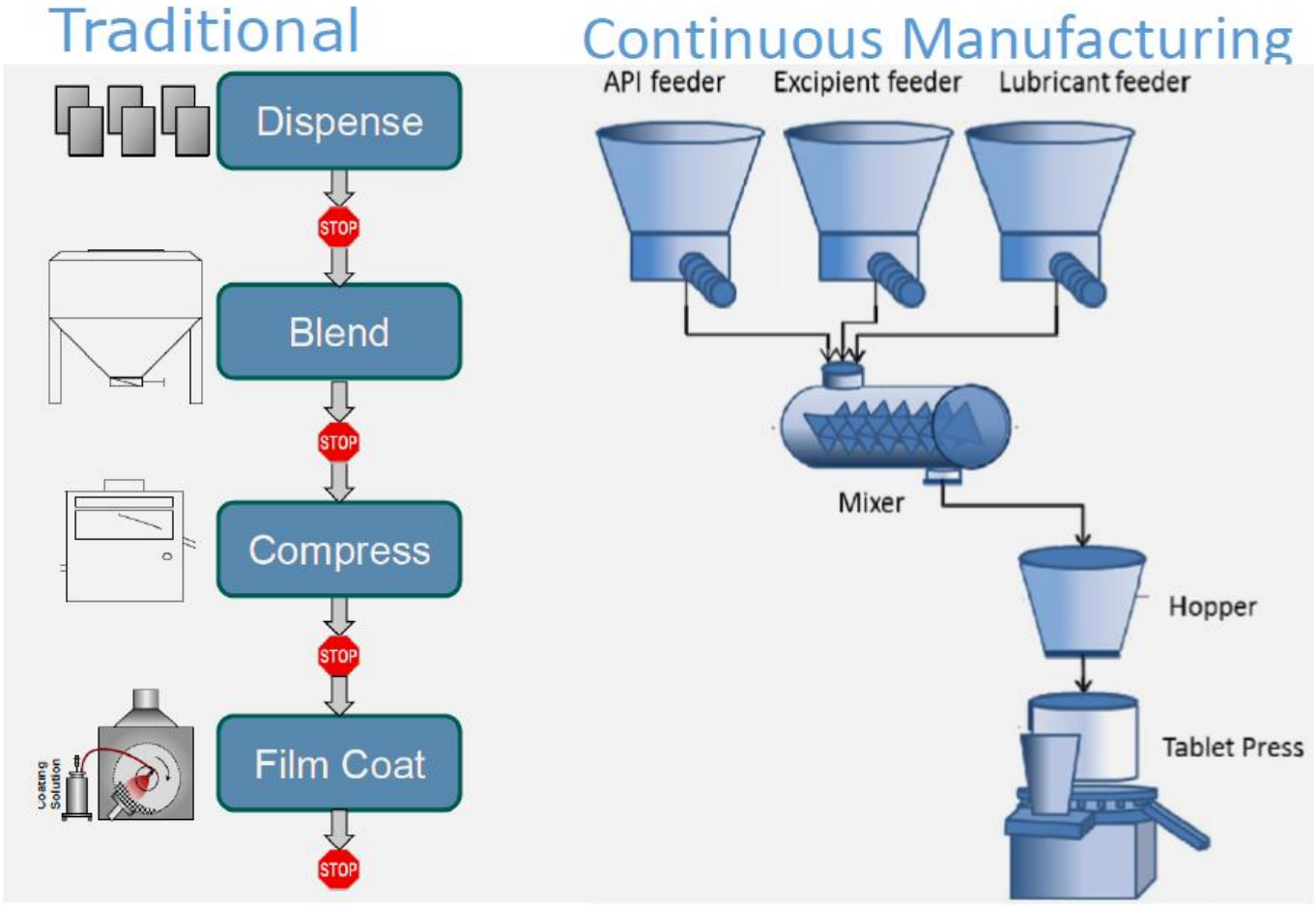
Rule of thumb: "Measure 6 times faster than the fastest expected change in the process"

Drug Release Performance / Pathways



Tablets – Mixture of Excipients & Active Pharm. Ingredients
Blend Uniformity Must be Controlled

Innovation from: Isolated (Batch/Traditional) to. Integrated Units (Continuous)



- System of integrated unit operations
- Tablets in < 5 mins
- Material moves IN/OUT continuously
- Driven by automatic controls
- Batch sizes flexible
  - Processing time
  - Produced / consumed kgs

The Engineering Research Center for Structured Organic Particulate Systems (C-SOPS)

- >$100 million in Federal & industry investment
- Number of papers published ~ 467
- Number of PhDs ~ 100
- Number of Postdocs > 35
- Research Staff - 7
- Number of faculty hired - 21
- Number of undergraduates in the lab > 150

RUTGERS THE STATE UNIVERSITY OF NEW JERSEY

NSF

NJIT New Jersey's Science & Technology University

PURDUE UNIVERSITY

RECINTO UNIVERSITARIO DE MAYAGUEZ UNIVERSIDAD DE PUERTO RICO CAAM

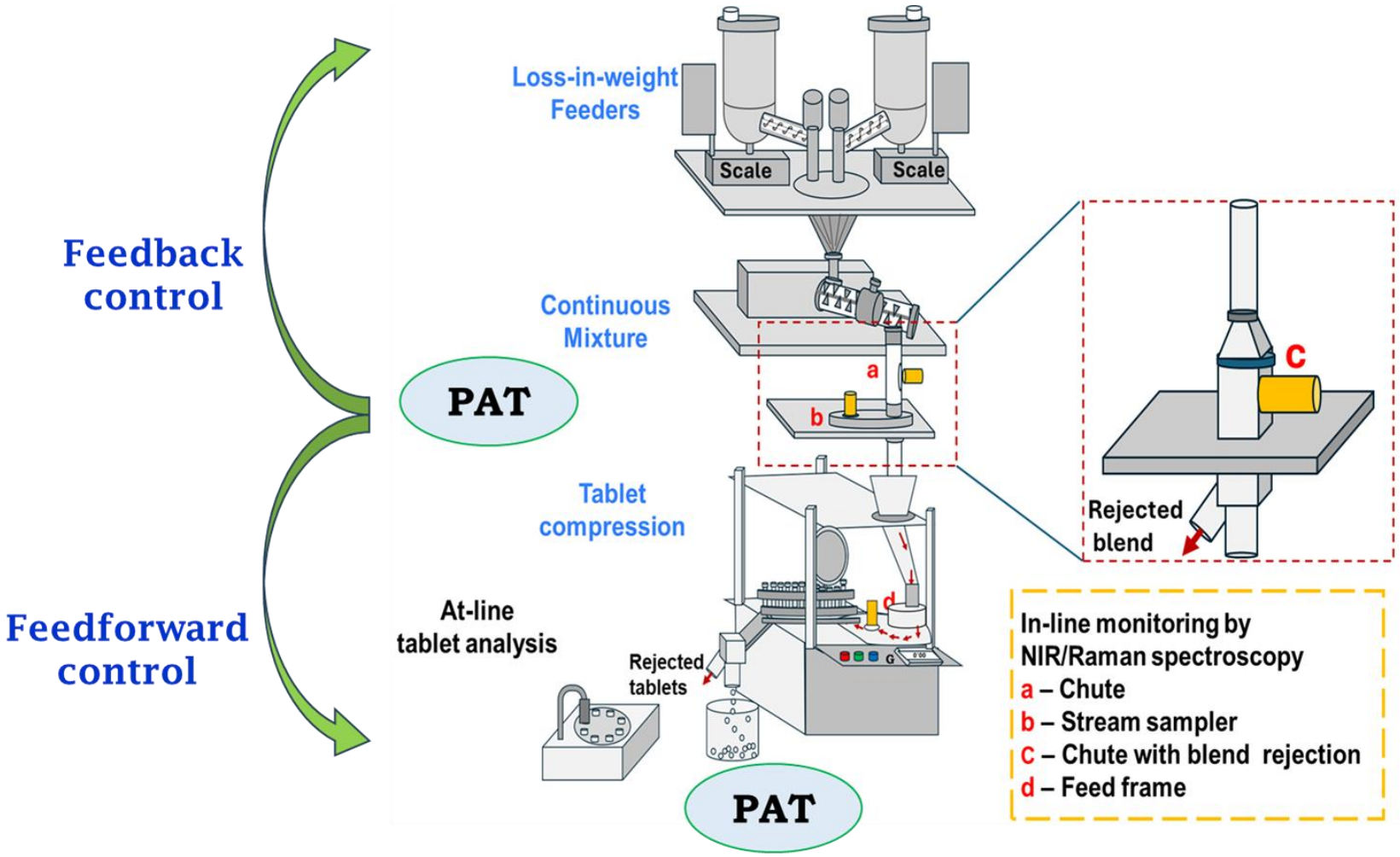
PAT & Continuous Manufacturing

Innovation

Chemists do not wait in lab for samples to arrive.

Chemist analyze flowing powder mixtures.

Chemists work with engineers to design systems for real time monitoring) & control of pharmaceutical processes.



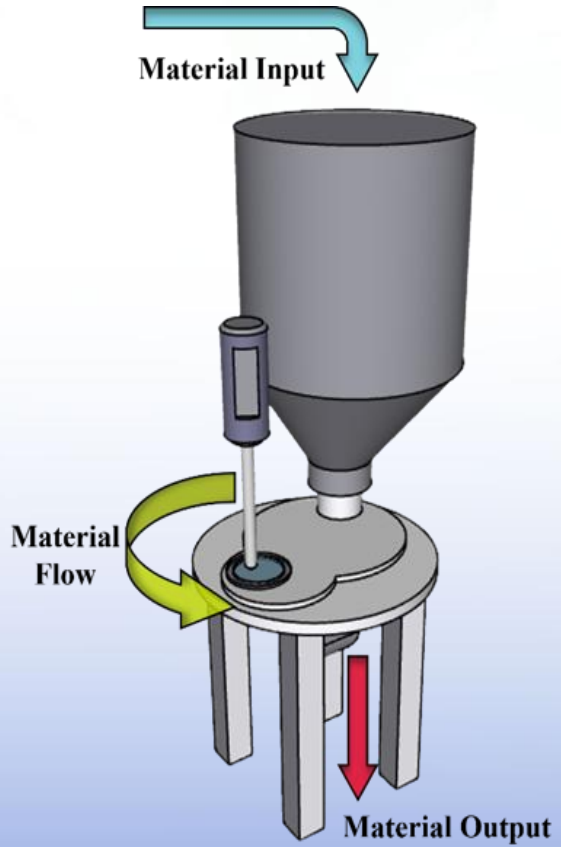
Movilla-Meza, N. A., Patel, D. S., Méndez, R., & **Romañach, R. J**. (2025). PAT for monitoring the state of control in continuous manufacturing of solid oral dosage forms. Analytical and Bioanalytical Chemistry. https://doi.org/10.1007/s00216-025-06012-w

SSK Powder Dynamics
(30 kg/hour – 5% Ibuprofen/Lactose/MCC)

Commercial product designed to:

- NIR or Raman spectra of flowing powders.
- Avoid particle rearrangement, attrition & affecting the blend.
- All parts of the lot have the same opportunity of being selected as a sample (Fundamental Sampling Principle)
- Avoid powder recirculation.
- Could be used with all tablet presses.

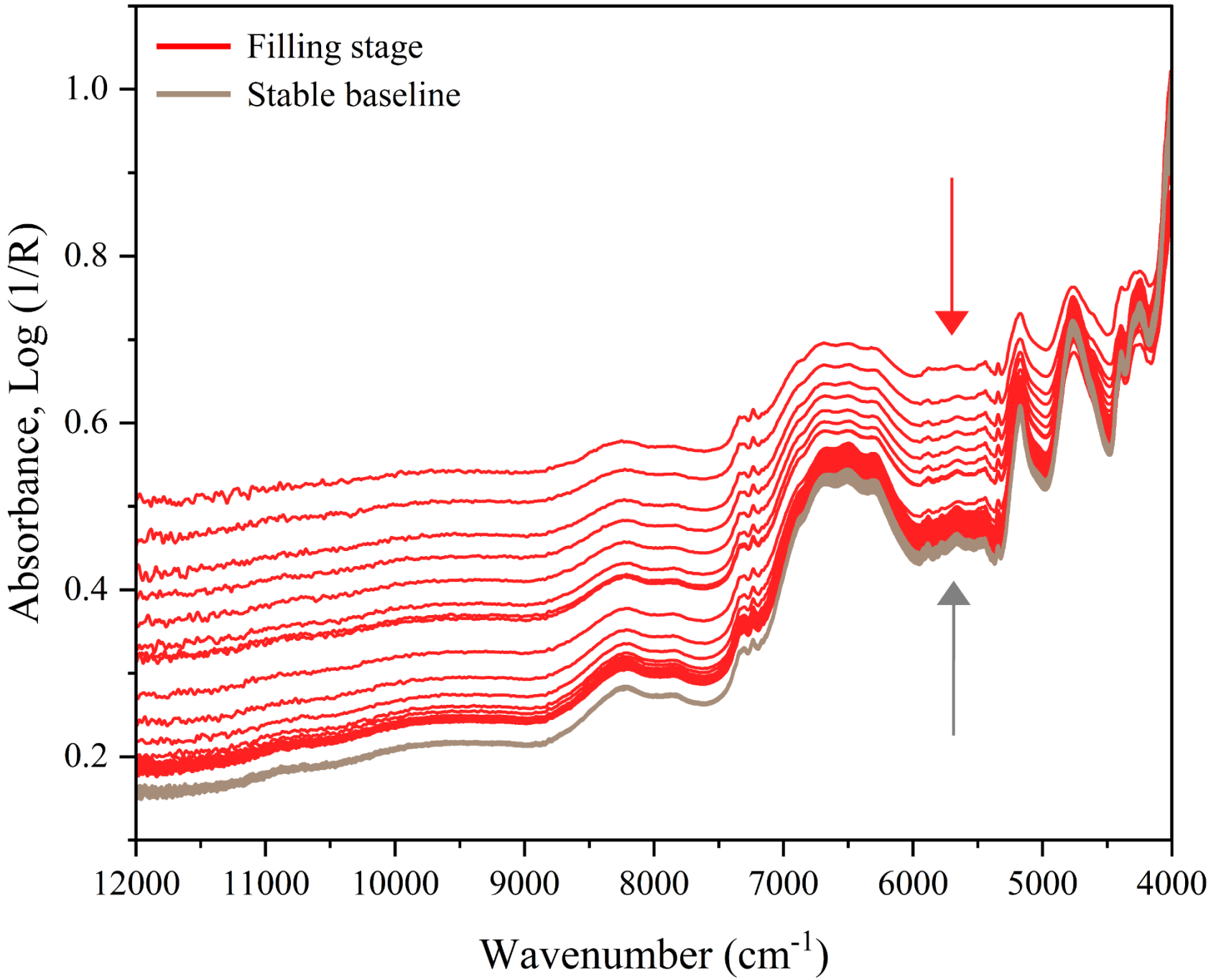
Stream Sampling Kit – Confined Powder Flow



US patent 10,520,400.

- Powder flows from hopper or Cont. mixer to the stream sampler
- Powder Confined within paddles (designed to eliminate wave pattern)
- NIR or Raman spectra obtained at 180° from inlet
- Powder leaves the system at 270° after its entry, avoiding recirculation (different from a Feed Frame)

Rangel-Gil, R. S., N. O. Sierra-Vega, R. J. Romañach and R. Méndez (2023). "Assessment of blend uniformity in a stream sampler device using Raman spectroscopy." International Journal of Pharmaceutics **639**: 122934.



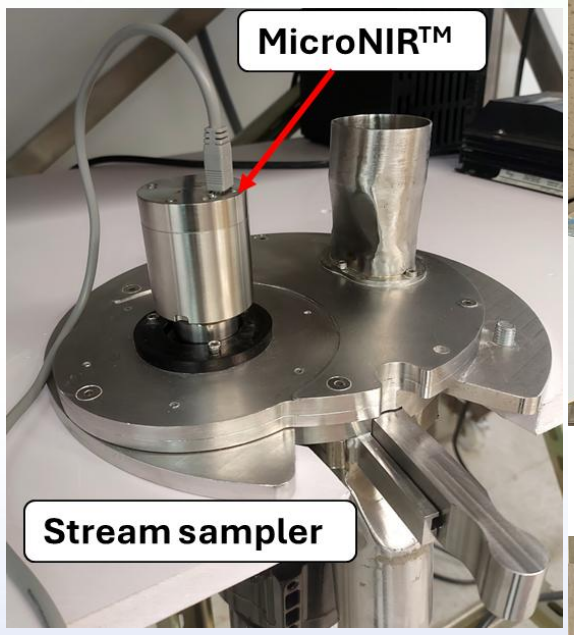
NIR spectra acquired for 5.00% w/w target conc. with mixer at 250 rpm & sampler at 6 rpm.

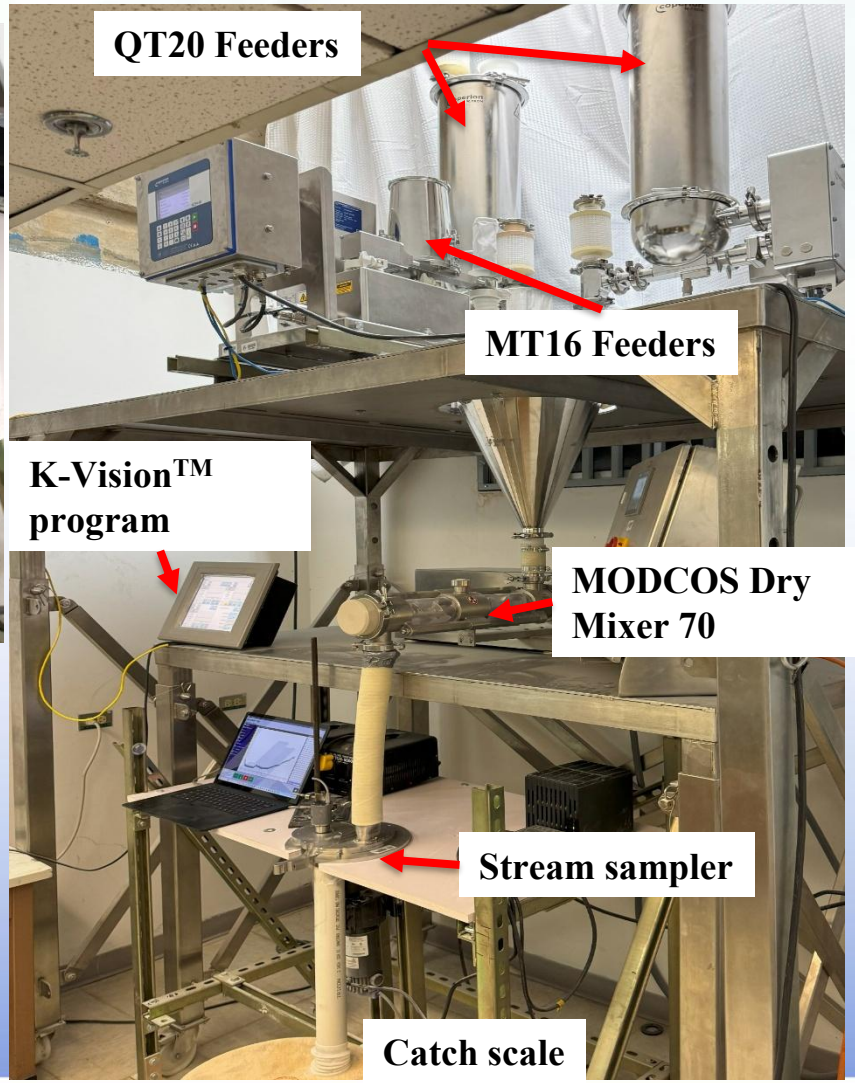
The red spectra correspond to the filling stage of the stream sampler - first 200 seconds of operation.

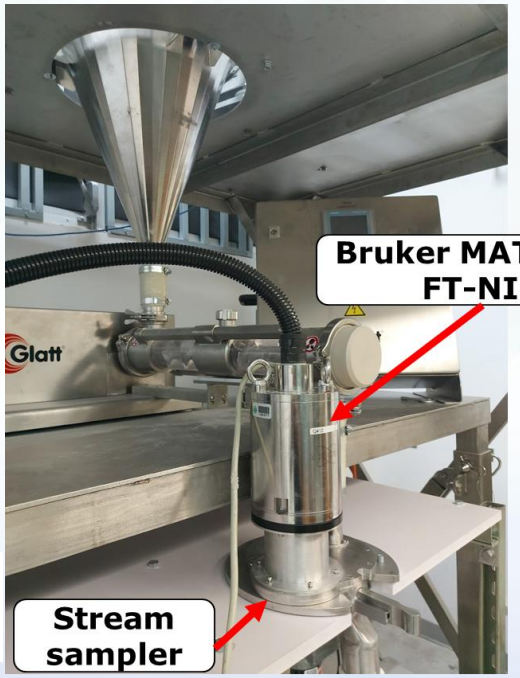
The 200 gray spectra were acquired during 5 min of operation.

International Journal of Pharmaceutics, *661*, 124478. https://doi.org/10.1016/j.ijpharm.2024.124478

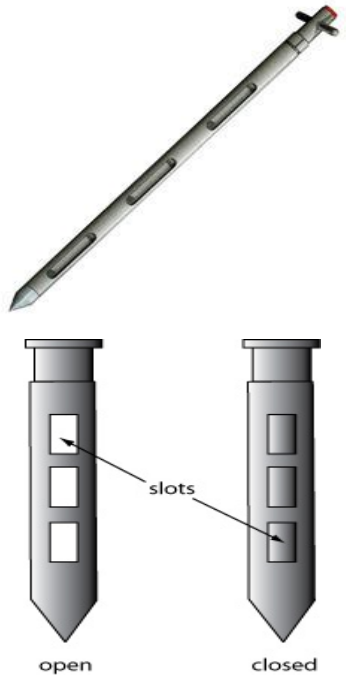
Stream Sampling in Continuous Mixing

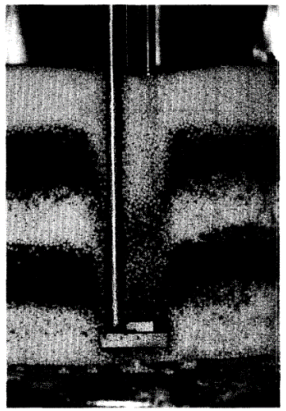




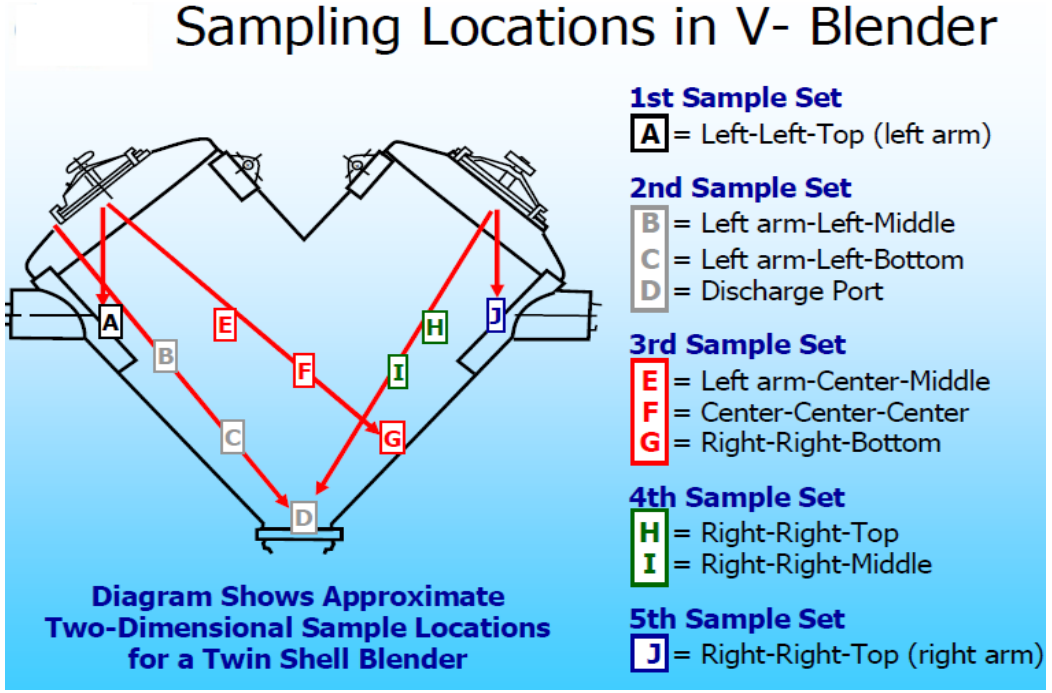


Current Sampling in Batch Manufacturing





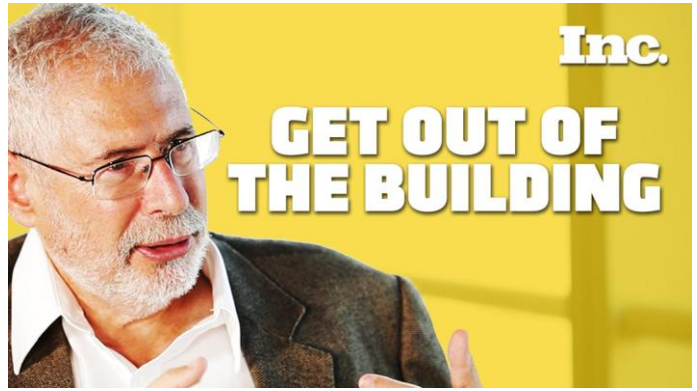
F.J. Muzzio et.al., International Journal of Pharmaceutics, 1997, 155, 153 – 178.



"All parts of the lot, do not have the same opportunity of being selected, and the powder mixture may be disturbed "

The National Science Foundation Innovation Corps (I-Corps) seeks to increase the economic impact of the research it has funded

- created by the NSF in 2011 to help move academic research it has funded to market.
- Participants are required to obtain evidence to quickly to learn whether or not their ideas are worth pursuing.
- Teams are expected to interview 100 potential customers, over the 6 - 10 week period.



Success starts with understanding your customers (students, researchers & industry

https://venturewell.org/i-corps/, accessed August 2025

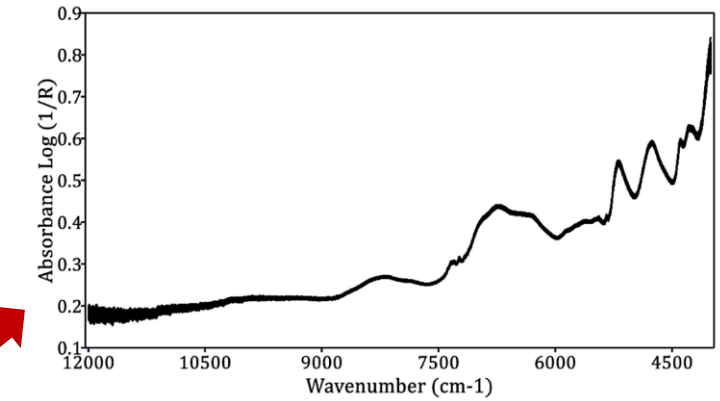
Results of I-Corps Interviews

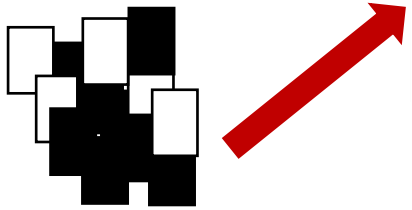
- > 250 interviews.
- ≈90% of products where thief is used meet specifications. Current industry view is that the thief is adequate in blends where components have similar particle size distribution.
- 5 companies willing to invest & change their procedures to reach market faster, and avoid future mfg problems.

Pinzon de la Rosa, C.; Rodriguez, V.; Hormaza, M. L.; **Romañach, R. J**. In *TOS MEETS THE NSF I-CORPS™ PROGRAM*, 8th World Conference on Sampling and Blending, Perth, Australia, Australian Institute of Mining and Metallurgy: Perth, Australia, 2017; pp 351-354.

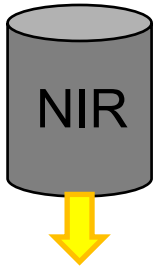
Composite Sampling Is possible with Real Time Spectroscopic Methods

Non – destructive
Real time NIR and Raman Spectroscopy

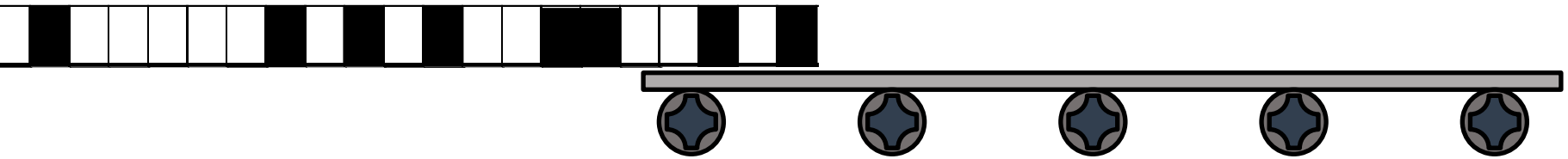




Spectrum is an average of 16 scans



16 scans per spectra
1.5sec



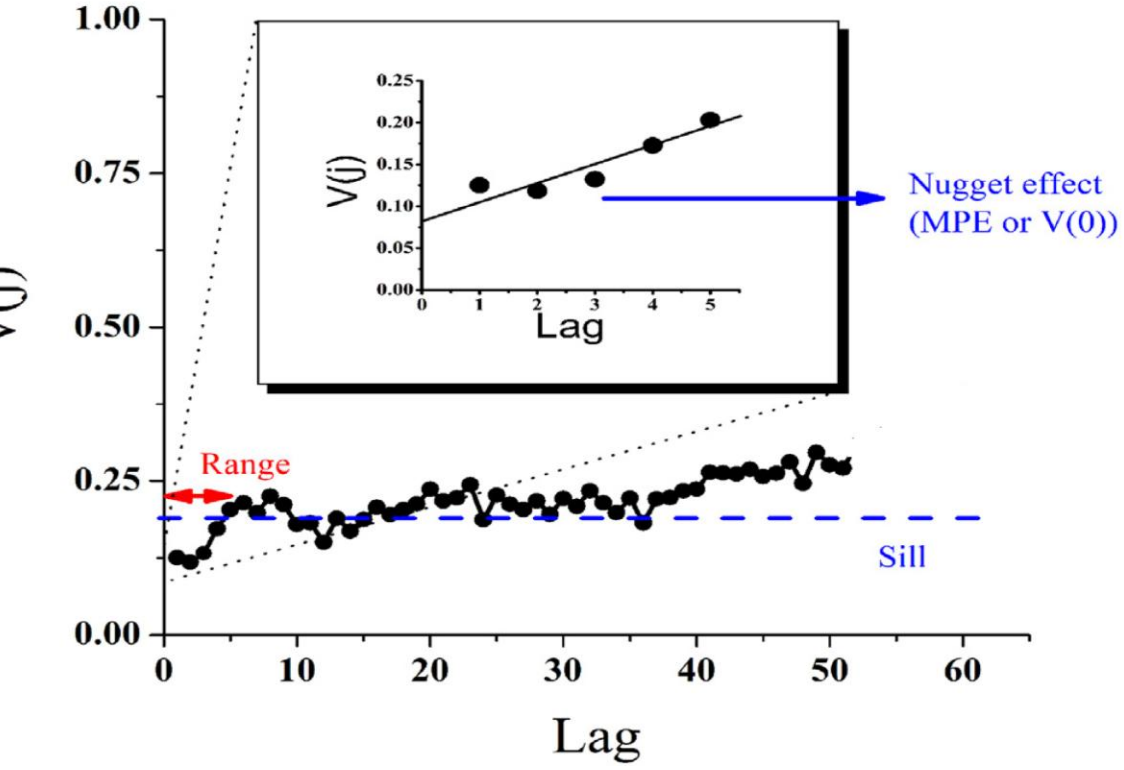
Lot Dimensionality Transformation (3D – 1D)

Also possible in pharma – powder blends must flow to tablet compressing machines.

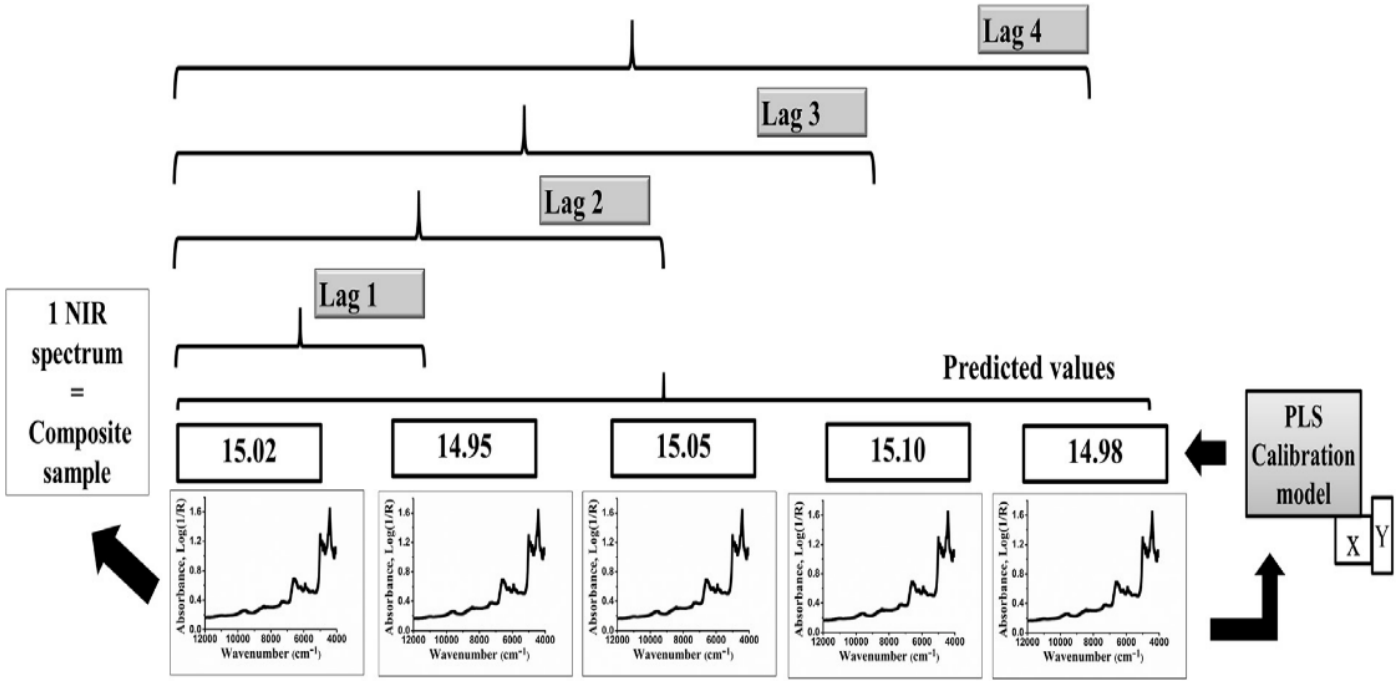
Petersen, L.; Minkkinen, P.; Esbensen, K. H., Representative sampling for reliable data analysis: Theory of Sampling. *Chemometrics Intellig. Lab. Syst.* **2005,** *77* (1–2), 261-277.

Esbensen, K. H., & Romañach, R. J. (2021). A Framework for Representative Sampling for NIR Analysis - Theory of Sampling (TOS). In E. Ciurczak, B. Igne, J. Workman, & D. Burns (Eds.), *Handbook of Near-Infrared Analysis* (Fourth Edition, pp. 415–461).

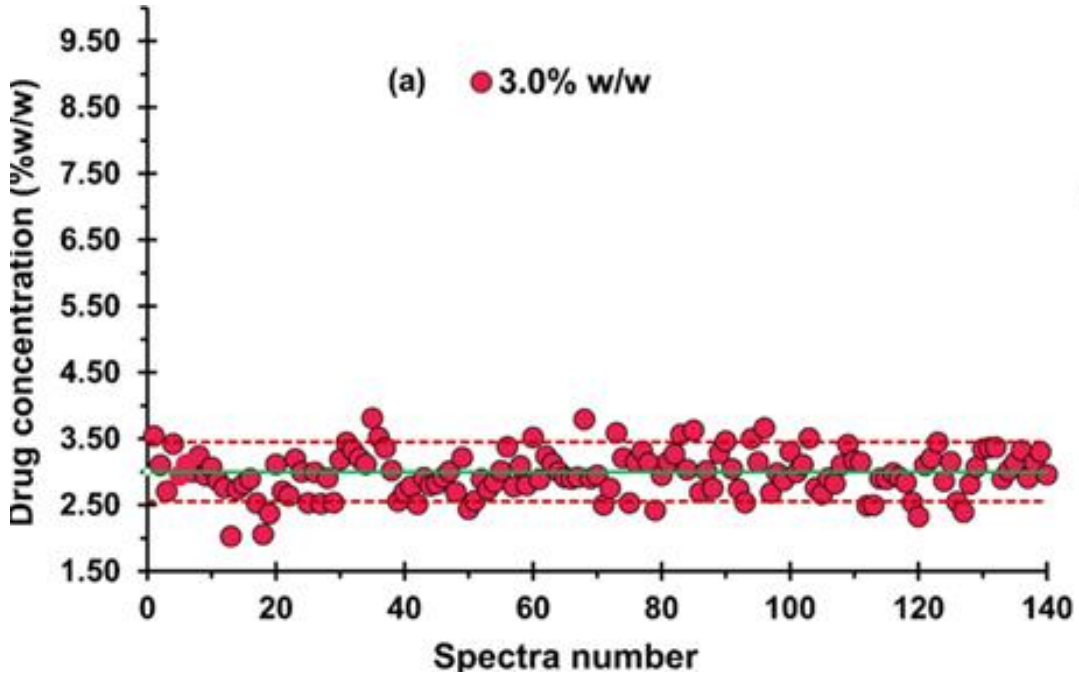
Variographic Analysis

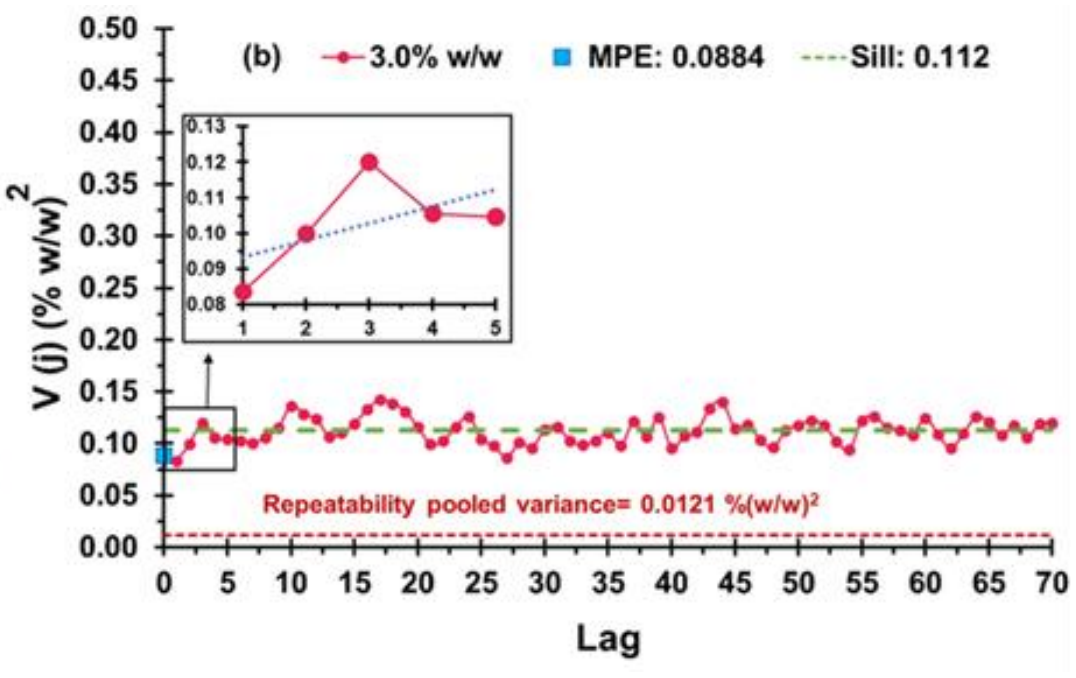


$$V(j) = \frac{1}{2(Q_{total} - j)} \sum_{q=1}^{Q_{total}-j} \left(h_{q+j} - h_q\right)^2$$



Computers & Chemical Engineering **2019,** *124*, 109-123.





Minimum Practical Error (MPE) – Sum of Sampling & Analytical Errors.
Sill – MPE = estimate of blend variance.
MPE/repeatability = (0.0884)/0.0121 ~ 7.3. Analytical error ~ 14%

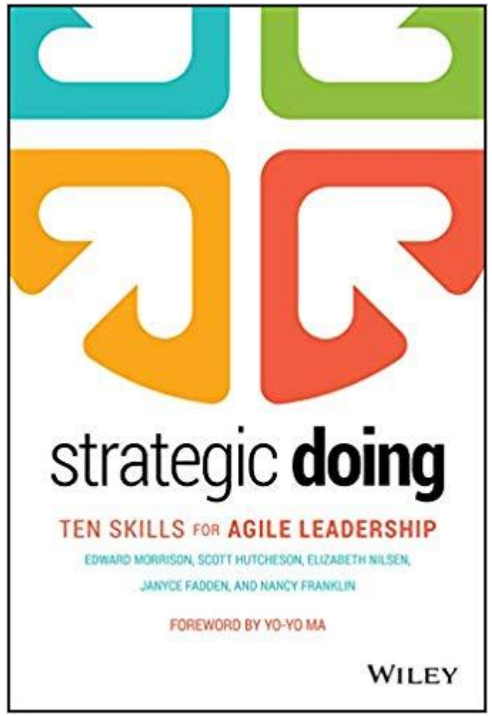
Movilla-Meza, N. A., Patel, D. S., Méndez, R., & **Romañach, R. J**. (2025). PAT for monitoring the state of control in continuous manufacturing of solid oral dosage forms. Analytical and Bioanalytical Chemistry. https://doi.org/10.1007/s00216-025-06012-w

Stream Sampler
Innovation with Scientific & Workforce Impact

- 9 peer reviewed publications
- 3 book chapters
- Contributed to the application of the Theory of Sampling in pharma mfg, & stimuli article on sampling in PAT in USP Pharmacoepial Forum.
- 4 Ph.D. students in Chemistry & 1 in Chemical Eng.
- 2 M.S. in Chemical Eng., 1 M.S. in Chemistry, & 1 M.S. in Industrial Engineering.

Strategic Doing

- Collaboration is a a psychological process.
- Need trust to think together to create new value.
- If we remember whose idea it was, we did not collaborate
- Need to think together in loosely connected networks where no one can tell anyone else what to do.
- Convincing is wasting time, let's think together.
- Strategic Doing enables people to form action-oriented collaborations quickly, move them toward measurable outcomes, and make adjustments along the way.



Success stories: Oklahoma City, Charleston Digital Corridor, Flint (MI), Milwaukee Water works,

https://agilestrategylab.org/about/

Morrison, E., Hutcheson, S., Nilsen, E., Fadden, J., Franklyn, N., 2019. Strategic Doing: Ten Skills for Agile Leadership. Wiley, page xxi, 151,

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