Feedback EMEA / Industry Discussion

Eli Lilly & Co Ltd Case Study:

Use of In-Line Near-Infrared Spectroscopy to Monitor Segregation of a Pharmaceutical Powder Blend in a Tablet Press

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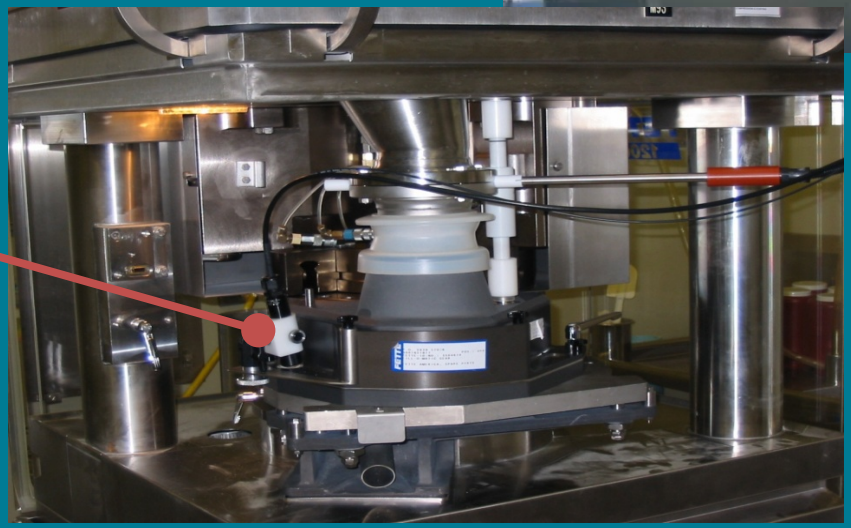
Case Study Summary

- Real time powder uniformity monitoring during compression
- Non-contact NIR probe

NIR probe positioned in Fill-o-matic Feeder Frame, prior to tablet compression. ~ 10 – 15 mm from tablet die.



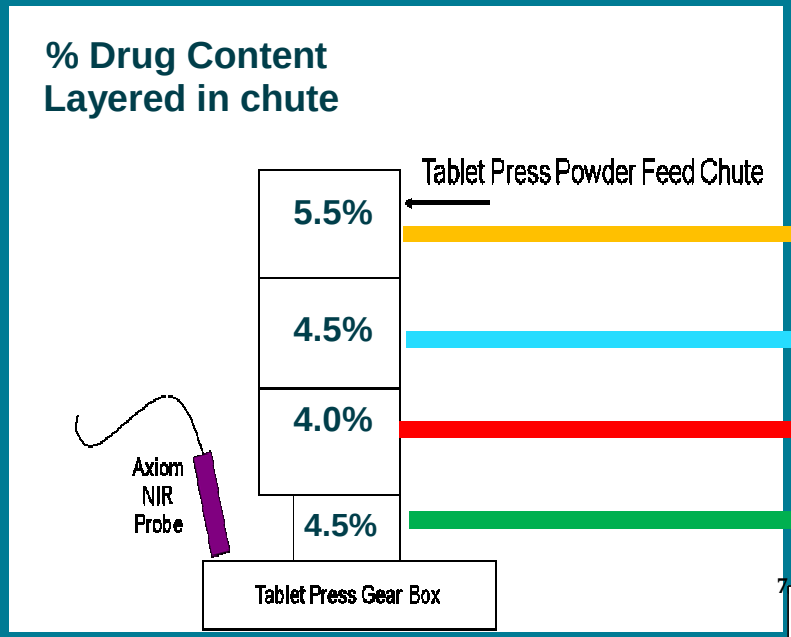
- Technique allows for :-
  - rapid & non-destructive content uniformity assessment
  - segregation determination of the blended materials, both API and excipients, going directly into the final pharmaceutical solid dosage form, i.e. tablet.

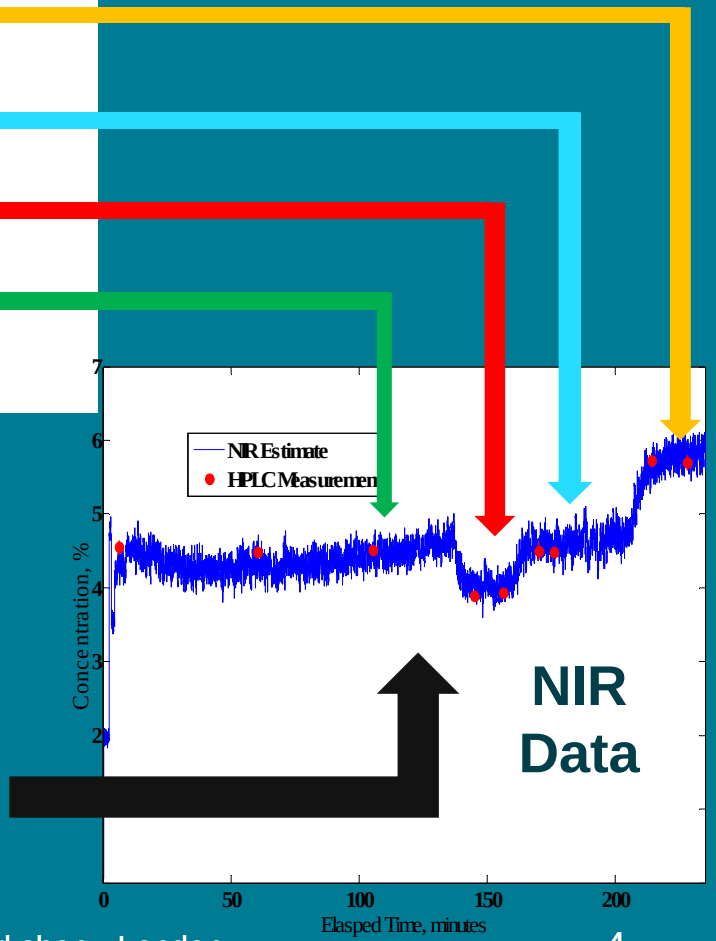
Case Study Summary

- NIR System - Rapid data acquisition times (<35 milliseconds per spectrum)
- Shown to provide an alternate strategy for demonstrating adequacy of mixing of powder blends
- Excellent potential to monitor a larger fraction of the entire blended sample preparation
  - Improved statistical description of variation within an entire production batch.
- Improvement on PQRI Draft Guidance recommendation
  - of using stratified sampling of both the blend and dosage units at specifically targeted locations

Case Study Summary

Layered powder fractions of differing concentration in tablet hopper





Accurate product monitoring in real-time throughout the batch

- **Conclusion**
  - In-line NIR method provides for an additional tool in the QbD/PAT tool box
  - Can be used to assess and identify critical sources of process and product variability
    - Eg correlating properties such as particle size, shape, density, surface texture, cohesiveness, etc. to powder flow and uniformity
  - Enables production of a more consistent product that meets predefined critical quality attributes.
  - With development may provide an opportunity for alternative product testing strategies

Main Topics Discussed

- **Technical questions**
- **Introduction of novel technologies**
  - Data required in submissions
  - When does “novel” become “platform”
- **Development – improving Process / Product Knowledge**
  - Traditional versus “monitoring” sampling techniques
  - Data presentation for assessment (quantity/section)
  - Bridging studies between traditional and novel techniques
  - Pure process knowledge information – does it need to be presented for review

Main Topics Discussed

- **Design space / Control strategy**
  - Data for process understanding / development purposes
  - Potential use as “real time release test”
- **Regulatory Framework**
  - Current regulatory framework changes needed to enable implementation
  - Provision of timely advice on new CMC approaches

Common Understanding

- NIR spectroscopy is a potential and suitable tool for controlling process and product quality
  - NIR could replace existing IPC
  - NIR could add to existing IPC to povide enhanced information on manufacturing process
- NIR measurement provides increased knowledge of process variability
  - Increased sampling frequency (continuous verification)
  - Does this provide a basis for changing conventional thinking and decision making ?
- EMEA NIR guidance is currently under review

Common Understanding

- Concept development
  - Potential for technique to replace end-product-testing (real time release testing)
  - Thorough risk assessment and evaluation needed
  - Understand key parameters
    - Eg impact of machine type, influence of excipients
- Dossier submissions for new technologies
  - Explain concepts, science and summarise key data
  - Supporting information eg spectra would be reviewed at inspection
- A PAT defined control strategy would need to be fully integrated into a Quality Management System
  - Eg . Atypical results, Out of specification process
  - Strategy may be specific to technology / technique

Areas for further work

- Defined structures for training and advice are necessary (industry and regulators)
    - e.g. workshops, presentation s on new PAT approaches
- Take opportunities for using EMEA PAT team and Scientific Advice procedures
    - accurate definitions, interactive dialogue, accepted agreements
- Regulatory guidance should be adjusted appropriately
    - e.g. Variations, NIR, RTR testing, process validation

Areas for further work

- Changing the perspective – different approaches may match or improve on traditional methods through analysis of different information
  - Eg Uniformity of dose could be replaced by continuous evaluation of powder blend uniformity and tablet weight
- "New" technology principles need to be explained
  - Statistical approaches
    - Ensure approaches (data filtering) are scientifically valid
      - Eg use of standard diagnostic techniques
    - How to demonstrate that the data analysis has looked at the positive and negative influences on the data set ?
    - Where best to describe data analysis models ?
  - Consider industry / regulator training programmes on specific techniques - Eg Multivariate data analysis

Conclusion

- In-line estimation of API concentration of a flowing powder in a tablet press has been demonstrated using a NIR probe and a good chemometric model.
- Further development may allow traditional control and testing strategies to be changed – continuous verification
- Successful development and implementation of such techniques will require discussion and adaptation of regulatory frameworks & submission content
- Regulators and industry share common views on what can be achieved – further discussion to allow successful implementation will continue