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Molecular Basis of Manufacturing

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Abstract

This paper describes the Biotechnology Innovation and Regulatory Science course named The Molecular Basis of Manufacturing. This course covers drug manufacture including excipients, basic formulation, basic DOE analysis, and analysis of the final drug product (typically tablets or capsules). Molecular interpretation of formulations is discussed. The modules in the course are described as well as other course materials including quizzes and discussion questions. This paper will assist with the development of course in this area throughout the entire world.

Description

This advanced laboratory course addresses important Statistics and Chemistry Manufacturing and Control (CMC) issues related to manufacturing and quality by design. The course provides important information on strategies for quality by design, manufacturing strategies for early development, the best approaches to analyzing data, and strategies for reporting the information to the FDA. This course will also focus on statistics, product design, and processing. Using statistics, product and process design helps achieve quality by design (QbD), strong development reports, and excellent regulatory submissions and allows continuous improvement. The course includes online material, laboratory exercises, and/or workshops outlining how to interpret the data.

Modern pharmaceutical companies must conduct drug discovery, development, manufacturing and marketing in a highly regulated environment with increasing competition and pricing pressures. Systems for quality manufacturing, quality by design of manufacturing processes, process analytical technology, statistical analysis, and on-line measurement are critical elements for success in this complex and evolving environment. The cost of poor quality and the penalties for non-compliance are unacceptable in today's drug development business. Knowledge of effective quality manufacturing principles and practices is critical to getting things *right the first time*. This course will provide information on best-in-class methods for quality manufacturing, quality by design and formulation.

The rationale of the course ties to the BIRS program's purpose. High quality and appropriate compliance (QA/QC) are essential for the viability of American industry, and academia as well. Almost daily, examples come to light showing the downside of poor quality or compliance: operations or organization closed, fines levied, careers affected, public images besmirched, credibility lost.

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Interestingly, in the pharmaceutical industry staff for QC and QA are most often recruited from operations areas; few have any formal education on the policy and regulations and core principles of their new professions…and

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most all have no detailed knowledge on specific skills for the job. In fact, only a few formal QA/QC education programs exist in America.

The initial target audience for Regulatory and Quality Compliance MS program includes:

- Regulatory affairs, quality control, or quality assurance professionals who are already in the field and seeking a continuing education experience in order to grow their knowledge or as a way to differentiate themselves from their counterparts in an organization
- Already degreed and working people who are seeking an opportunity to explore a new career or to train to make themselves more competitive to enter a quality-related career

This course is aimed at graduates from STEM content backgrounds and expertise. The course addresses sophisticated biotechnology innovation issues and FDA regulations in a range of areas including Safety, Toxicology, and Chemistry Manufacturing and Control. The course is at the MS level.

Intended Teaching Setting

The intended teaching setting for this course is online with one weekend of laboratory experiments.

Course Project Modules

- Big questions for Developing a Candidate through Proof of Concept
- Overview of Pharmaceutical Unit Operations-Drug Product
- Mixing
- Flow and Blending
- Particle Size Reduction
- Introduction to Drying Basics
- Granulation
- Tablet Compression
- Tablet analysis
- Coating
- QbD Concepts: Science of Design and the Socratic Review
- ICH and International Thinking on Quality by Design & Development
- Development Report
- ICH Q9 Quality Risk Management
- Quality Systems
- Introduction to API Management
- API Crystallization
- API Synthesis, Isolation, & Drying
- Impurities
- Residual Solvents in API Manufacturing
- Powders & Mechanical Properties
- Hard Shell Gelatin Capsules
- Powder Formulations
- Process Validation
- Cleaning Verification in Pharmaceutical Manufacturing
- Method Validation SOP
- Solubility and Dissolution Testing
- Dissolution Methods Validation ANDA Section XV Dissolution
- API Certificate of Analysis
- Certificate of Analysis Drug Product
- Validation of PAT Methods

Learning Activities

Students will complete approximately 16 contact hours of laboratory work. They will carry out a complete manufacturing process in the College of Pharmacy's pilot-scale manufacturing lab. The process will include various unit operations, blending, wet granulation, drying, tableting and coating. Participants use on-line NIR to monitor some of these unit operations and will use Chemometrics to analyze some of the on-line data. In addition, various off-line techniques will be used or demonstrated. The goal is to provide enough information to allow the student to apply their acquired skills in the place of work.

Reading List

Students will utilize The Theory and Practice of Industrial Pharmacy by L. Lachman, H. A. Lieberman and J.L. Kanig, Lippincott-Stipes as well as a manual containing all the presentation slides used for the course. A lab notebook, "Introduction to Pharmaceutical Unit Operations", will be utilized for the laboratory weekend.

Library Resources

Additional use is made of primary literature sources and electronic documents available on the Purdue Libraries web site including Pub Med, the USP, Merck Index, and Sci Finder.

Example of a Module

1. **TLI 525 Molecular Basis of Manufacturing**
2. **Advanced Granulation**
   - See Ch. 20, Granulation Rate Processes by Hapgood and Litster in Granulation Edited by Salmen, Hounslow and Seville
   - Also see slides from lectures by J. Litster at Purdue University
3. **Granulation Rate Processes**
   - Three processes occurring simultaneously:
     - *Nucleation*
     - *Consolidation and Growth*
     - *Breakage*
4. **Four steps in nucleation**
5. **Ideal Nucleation Conditions**
   - Controlled nucleation occurs in *drop controlled regime* where 1 drop = 1 nucleus:
     - drop wets into bed completely before mixing causes contact with other partially wetted drops
     - drop overlap on powder surface is minimal
   - If spray drops coalesce, good mixing is required to disperse the binder (*mechanical dispersion regime*)
6. **Effect of Spray Drop Size on Nuclei Size**
7. **Granule consolidation**
   Without simultaneous drying, granules gradually consolidate towards a minimum porosity
8. **Coalescence Models**
9. **Effect of Impeller Speed on Granule Size**
10. **Hints for controlling wetting and nucleation**

Sample Quiz

(Answers bolded and underlined)

Quiz 4
Lectures 201-403
TLI 525 Molecular Basis of Manufacturing

1. Why is HPLC so widely used:
   a) Fast
   b) Provides enhanced separations
   c) Can be quantitative
   d) Works for most drugs
   e) <u>All are reasons</u>

2. HPLC is not used in:
   a) <u>Metal analysis</u>
   b) Pharmaceuticals
   c) Environmental
   d) Clinical
   e) Foods

3. A unit cell:
   a) Is created by electrons bombarding an anode
   b) <u>Is the smallest building block of a crystal</u>
   c) Is called Bragg's law
   d) Is chemically reactive
   e) All are correct

4. Which is not true about X-ray powder diffraction?
   a) primary method to determine crystal form using powder samples
   b) distinguishes between crystalline and amorphous materials
   c) further information is needed to fully characterize system: hydrate or solvate? transformation to another form?
   d) can be used to determine if samples are the same crystal form
   e) non-destructive: material can be recovered
   f) particle size, morphology, sample size can affect powder patterns based on preferred orientation
   g) temperature can be controlled for variable temperature studies
   h) can be used for qualitative or quantitative analysis
   i) <u>all are true</u>

5. Which is not true about Raman spectroscopy?
   a) Symmetric, non-polar groups are stronger scatterers
   b) Sharp, distinct bands
   c) Non-destructive
   d) <u>Depends on change in dipole moment</u>
   e) All are true

6. Chemical imaging cannot:
   a) Provide a way to determine heterogeneity of samples
   b) Can determine spatial distribution of every formulation component
   c) Can help differentiate tablets with the same chemical content (same assay) but different distribution of components and even different distribution of solid forms
   d) <u>Provide elemental analysis\</u>
   e) All are true

7. Which technique is not used for mixture analysis in the solid state?
   a) X-ray powder diffraction (XRPD)
   b) differential scanning calorimetry (DSC)
   c) infrared spectroscopy (IR)

d) Raman spectroscopy
e) solid-state nuclear magnetic resonance (SSNMR)
f) <u>All are used</u>

8. Quantitative analysis involves showing that which of the following criteria are met?
   a) specificity
   b) linearity
   c) range
   d) accuracy
   e) precision
   f) detection limit
   g) quantitation limit
   h) robustness
   i) <u>All of the above criteria must be met</u>

9. Which is not true about quantitative Raman spectroscopic methods?
   a) Raman is applicable to drug substance and product
   b) No major sample preparation required
   c) Possible thermal degradation by laser irradiation
   d) Neat sampling allows recovery of the material
   e) Instrument variability day-to-day
   f) Moderate to long method development time
   g) <u>Very sensitive to water bands and presence</u>

10. The Noyes Whitney equation says:
   a) <u>Concentration is a function of surface area</u>
   b) Concentration decreases with time
   c) Disintegration is inversely proportional to dissolution
   d) There is no stagnant diffusion layer
   e) All of the above

11. Which is not a principle of validation?
   a) Planning, organizing and performing process validation
   b) Process validation protocols
   c) Data collected and reviewed against predetermined acceptance criteria – recorded in validation report
   d) Documented evidence: Process is capable of reliably and repeatedly rendering a product of the required quality
   e) <u>All are principles of validation</u>

12. Which is not a step in Hazard Analysis and Critical Control Points?
   a) Define the process and determine where risks to failure occur and identify potential preventative measures
   b) Identify Process Critical Control Points (PCCP) – must include steps that produce variability in final product
   c) Assign limits to PCCPs
   d) Establish monitoring requirements for PCCPs
   e) Determine actions to take when a PCCP limit is exceeded
   f) <u>Determine the dose of the drug</u>
   g) Establish a procedure for verification
   h) Establish procedures for effective record keeping

13. Which is not a criterial providing a rational conclusion of whether the process consistently produces quality products?
   a) A description of the statistical methods to be used in analyzing all collected data (e.g., statistical metrics defining both intra-batch and inter-batch variability).

b) Provision for addressing deviations from expected conditions and handling of nonconforming data. Data should not be excluded from further consideration in terms of PQ without a documented, science-based justification.
c) Design of facilities and the qualification of utilities and equipment, personnel training and qualification, and verification of material sources (components and container/closures), if not previously accomplished.
d) Determination of the risk of failure
e) Status of the validation of analytical methods used in measuring the process, in-process materials, and the product.
f) Review and approval by appropriate departments and the quality unit.

14. Your DOE experiment showed which of the following were critical parameters (critical control points):
a) Amount of water
b) Binder amount
c) Particle size of active
d) Both a and b
e) Bothe b and c

15. For validation, tablet compression parameter do not include:
a) Mass
b) Hardness
c) Moisture
d) Friability
e) Disintegration
f) Dissolution
g) Thickness
h) All are included

16. Tests (methods) to be validated include
a) identification tests
b) assay of drug substances and pharmaceutical products
c) content of impurities and limit tests for impurities
d) dissolution testing and determination of particle size
e) all are included

17. Method validation for dissolution does not include:
a) Linearity and range
b) Injection precision
c) Spectroscopic calibration
d) Dissolution profile at 15, 30, 45 and 60 min.
e) Ruggedness
f) Filter recovery

Sample Case Study

Case Study. DOE Results
TLI 525. Molecular Basis for Manufacturing
Sept. 17, 2015

1. Analyze the percent release data and determine the effect of the following variables on percent release:
    a. MCC (101 vs 102)
    b. Binder amount (2,4)
    c. Wet massing (Y or N)
    d. Liquid amount (20, 30 or 40)

2. Explain your results

Case Study Low Assay

Fall Semester 2015

A paracetamol manufacturer notices that four replicates for the assay averaged 88.6%. In addition the dissolution level at Q 60 remained near 100%. Suggest a strategy to investigate this discrepancy. Limit your response to 3 pages.

Instructor Guide

- The course should cover 15 weeks
- Spread the modules (PowerPoints) evenly thought the weeks
- Include low stakes quizzes for each module
- Meet regularly on Zoom with students (once every two weeks) to go over main points of modules
- Assign three case studies throughout the course
- Final grade is based on three case studies (75%), quizzes 15% and participation during Zoom meetings 10%

Acknowledgement

This course has been taught for twenty years as part of several curricula at Purdue University and in Africa. Each of the many participant instructors contributed to this course in some way. We acknowledge all of their input and expertise. Without their input this course would not have been possible.