BEST PRACTICES IN ANALYTICAL DEVELOPMENT

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IMPORTANT ELEMENTS OF CONSIDERATION DURING PRODUCT DEVELOPMENT

- Define the target product profile
- Identify critical quality attributes
- Fix the quality attributes of drug substances, excipients
- Define stages in mfg process for critical control strategy

CONTROL STAGES DURING PRODUCT DEVELOPMENT

- Drug Substances
- Excipients
- Container closure system
- Manufacturing Process

Aim : To design a quality product and its mfg process to consistently deliver the intended performance of the product.

ANALYTICAL DEVELOPMENT

- Involves tests procedures at each control stage:
  - Design
  - Development
  - In-process controls
  - GMP controls
  - Process Validation
  - Specifications
  - Product Release
  - Shelf Life studies

ANALYTICAL DEVELOPMENT – DRUG SUBSTANCE

- Critical Quality Attributes (CQAs)
  - A CQA is a physical, chemical, biological or microbiological property that needs to be with in the acceptance criteria set appropriately to ensure desired product quality
  - Include properties that affect identity, purity, biological activity & stability

ANALYTICAL DEVELOPMENT – DRUG SUBSTANCE

- CQAs provide
  - A link for Material Attributes & Process Parameters
  - Identify potential material attributes to be controlled (e.g. Specific RM or Intermediate)
  - Identify potential process parameter to be addressed by control strategy
- Defined CQAs demand appropriate Method

ANALYTICAL DEVELOPMENT – DRUG SUBSTANCE

- Important Features
  - The route of synthesis
  - Molecular structure & Functional groups
  - Estimate pka value
  - Solubility
  - UV/Visible spectrum
  - Characterization of each stages

ROUTE OF SYNTHESIS

- Raw Materials
- Potential Impurities from RM
- Intermediate Stages
  - Isolated
  - In Situ
- Solvents used in all stages
- Possible bye products and degradants
- Time available Vs. Importance of analysis objective

MOLECULAR STRUCTURE & FUNCTIONAL GROUPS

- Provides direction for method to be developed
- Idea about chiral nature

E.g Primary / Secondary amines

- Non aq titration

Tertiary amines

- Colour development with acid dye's

Unsaturated groups

- UV detection

Saturated molecule without strong ionic

pKa VALUE, SOLUBILITY & UV/VIS SPECTRA

- Important w.r.to HPLC method
- Decide suitable Mobile phase pH
- Suitable wavelength of detection
- Suitable mobile phase ingredients

CHARACTERIZATION OF STAGES

- Control of quality of RM

- Control of quality for Intermediates
  - Useful in process optimization w.r.to time of reaction, temperature, mole ratio of solvents /reagents / catalysts
  - Helps in achieving optimum process time & yield
  - Helps in finding route cause for impurities in final product

CRUCIAL PHYSICAL CHARACTERISTICS – DRUG SUBSTANCE

- Polymorphism
  - FTIR , DSC, XRD, Solid state NMR
- Particle size
  - Affects drug release from Drug Product

ANALYTICAL DEVELOPMENT – DRUG PRODUCT

- Critical Quality Attributes
  - Assay
  - Related Substances
  - Dissolution
  - Uniformity of Dosage units
  - Disintegration Time

ASSAY OF DRUG PRODUCT

- Stability indicating method
- Sample preparation
- Specificity, Solution stability, Filter validation, Recovery
- Robustness
  - Column to column
  - Equipment of different make
  - Lab to Lab
- Evaluate chromatography, results throughout product development stages

RELATED SUBSTANCES TEST

- Specified impurities
- Unidentified impurities
- Degradation products
- Specific impurities

DISSOLUTION

- A Single most important test that will ensure the quality of a product w.r.to efficacy.
- In-vitro dissolution standards reflect in vivo drug performance
- Provides means to evaluate adequate bioavailability from batch to batch
- Provides information necessary to the formulator in development of more efficacious and therapeutically optimal dosage

DISSOLUTION

- The process by which a solid substance enters in the solvent to yield a solution.

- Factors affecting dissolution test
  - Rate of the processes of disintegration
  - Rate of deaggregation
  - Rate of intrinsic dissolution

These processes depend on the composition

FACTORS AFFECTING THE DISSOLUTION RATE

- Physicochemical properties of the drug substances
- Related to drug product formulation
- Related to dosage form
- Related to dissolution testing device
- Related to dissolution test parameters
- Miscellaneous

FACTORS RELATED TO PHYSICOCHEMICAL PROPERTIES OF THE DRUG SUBSTANCE

- Factors affecting solubility
  - Polymorphism
  - Amorphous state and solvation
  - Free acid, free base or salt form
  - Complexation, solid solutions and eutectics
  - Particle size
  - Surfactants
- Factors affecting surface area available for dissolution
  - Particle size

FACTORS RELATED TO COMPOSITION AND METHOD OF MANUFACTURE FOR TABLETS

- Amount and type of diluent or filler
- Type of tablet manufacture employed
- Granule size and size distribution
- Amount and type of disintegrants and method of incorporating it
- Amount and type of surfactant
- Compression force and speed of compression

FACTORS RELATED TO COMPOSITION AND METHOD OF MANUFACTURE FOR CAPSULES

- Amount and type of diluent or filler
- Method used to reduce bulk

  (e.g granulating and Slugging)
- Granule or powder size and size distribution
- Amount and type of lubricant and method of incorporating it
- Amount and type of surfactant

FACTORS - MISCELLANEOUS

- Adsorption
- Sorption
- Humidity
- Detection Errors at the time of Method Transfers

FACTORS – TESTING DEVICE

Variable	Max Allowed	Excess Commonly Seen	Effect of Excess	Methods of Control
Vibration	0.1 mil displacement	0.2 – 0.9 mil	+ 5 – 10%	Eliminate source
Alignment	1.5° to perpendicular	2 - 7°	+ 2 – 25%	Adjust alignment
Centering	± 2 mm	± 2 – 6 mm	± 2 – 13%	Center individual vessel
Dissolved gas	Deaerated	Bubbles form	± 50%	Effectively De-aerate media
Media pH	0.00 accuracy	± 0.05	± 10%	Control pH
Sampling Position	Compendium	± 0.5 cm	Little	Use Care

ANALYTICAL DEVELOPMENT DURING PRODUCT DEVELOPMENT

Salient features of the topic:

- The methods development is a continual improvement program
- The methods are finalized after validation in the form of specifications
- Method Transfer should be a smooth process

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THANK YOU