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M.Pharm Practical Notes

Pharmaceutical Quality Assurance Practicals I

Semester 1

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UV-Visible Assay of Bulk and Formulated Drugs

Practical 1 - Bench practical

Aim

To determine drug content in a pharmaceutical preparation using a calibrated UV-visible response and a documented extraction and dilution scheme.

Principle

For a suitably dilute absorbing solution, absorbance is proportional to concentration and optical path length within the established working range. A calibration relates measured response to known concentrations in the selected solvent.

A formulation assay also depends on extraction recovery, specificity against excipients and correct dilution arithmetic. The wavelength and extraction conditions are selected from the adopted monograph or validated laboratory method; they are not universal for all drugs.

Materials and Requirements

- UV-visible spectrophotometer with suitable matched cells
- Certified drug reference material with stated potency
- Calibrated balance and volumetric glassware
- Method-specified solvent, filters and placebo where available

Procedure

1. Record analyte, product strength, batch, reference potency, solvent, wavelength, cell path length and method version.
2. Prepare a reference stock by accurate weighing and quantitative transfer. Correct its concentration for the stated reference potency once.
3. Prepare at least five calibration levels spanning the expected test concentration and a solvent blank. Use independently prepared check material when available.
4. Determine average dosage-unit mass when the method calls for a composite. Weigh a portion corresponding to the target analyte mass and extract using the adopted method.
5. Clarify the extract by a qualified process and make the final volume. Record every aliquot and dilution; assess filtration recovery where required.
6. Blank the instrument, measure calibration and test preparations, and inspect the spectrum for unexpected absorption or baseline effects.
7. Calculate the concentration from the fitted response, reverse the dilutions, and express content per unit and percentage of label claim. Retain raw spectra and replicate results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Preparation	Concentration or mass	Absorbance	Replicate / comment
Blank	0	Record	Solvent baseline
Standard levels	Record each level	Record	Calibration
Independent check	Record	Record	Accuracy check

Preparation	Concentration or mass	Absorbance	Replicate / comment
Test preparations	Record portion and dilution	Record	Prepare independently

Calculations

- A = mC + b; C = (A - b) / m
- Drug mass in extract (mg) = C_working (micrograms/mL) x dilution factor x extract volume (mL) / 1000
- Content per tablet = drug mass in portion x average tablet mass / powder portion mass

Worked Example

Illustrative data: a tablet weighs 500 mg and contains a labelled 100 mg drug. A 250 mg powder portion represents 50 mg nominal drug.

The portion is extracted to 100 mL. Diluting 1 mL to 100 mL gives a dilution factor of 100.

Calibration: A = 0.100C + 0.002, with C in micrograms/mL. Test absorbance 0.492 gives C = 4.90 micrograms/mL.

Extracted drug = 4.90 x 100 x 100 / 1000 = 49.0 mg. Content per tablet = 49.0 x 500 / 250 = 98.0 mg, or 98.0% of label claim.

Result and Interpretation

- Enter the actual assay with replicate variability and the applicable product specification.
- A good linear fit alone does not establish specificity, extraction completeness or suitability for release testing.
- Document any dilution outside the calibrated range and prepare an appropriate fresh dilution.

Precautions

- Use the solvent blank and cell type required for the spectral region.
- Avoid fingerprints, bubbles and suspended particles in the optical path.
- Confirm solution stability and extraction recovery before interpreting low recovery as low product content.
- Apply reference potency and dilution factors once, with units at each step.

Viva Questions and Answers

Why is placebo comparison useful?

It reveals absorption or extraction effects from ingredients other than the analyte.

Why prepare separate test solutions?

Independent preparations include weighing and extraction variability, unlike repeated readings of one solution.

Can any wavelength give the same assay?

The wavelength must provide suitable sensitivity and selectivity under the validated conditions.

Simultaneous UV Estimation of Two Components

Practical 2 - Bench practical

Aim

To estimate two absorbing components from their combined absorbances at two suitable wavelengths.

Principle

At each selected wavelength, the total absorbance is the sum of the individual component contributions when the solutions obey linear response and the components do not interact spectrally.

Two independent equations can therefore resolve two concentrations. The coefficients must be established for the actual solvent, pH, path length and concentration units; a nearly singular coefficient matrix gives unstable estimates.

Materials and Requirements

- UV-visible spectrophotometer and matched cells
- Separate reference materials for both components
- Solvent blank and formulation placebo
- Volumetric glassware and a prepared mixture

Procedure

1. Scan the pure components and select wavelengths with sufficiently different relative responses.
2. Prepare separate calibration series for each component at both wavelengths. Record slopes and intercept treatment.
3. Verify that the working range is linear and that a prepared mixture behaves approximately additively.
4. Prepare and clarify the formulation extract. Dilute so both components lie in their established ranges.
5. Measure the blank-corrected mixture absorbances at both wavelengths, using the same cells and settings as calibration.
6. Solve the simultaneous equations and reverse the extraction and dilution scheme for each component.
7. Confirm performance using known mixed standards, recoveries and independently prepared test solutions. Review any negative or implausible concentration before reporting.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Preparation	A at wavelength 1	A at wavelength 2	Calculated X and Y
Pure X levels	Record	Record	Coefficient estimation
Pure Y levels	Record	Record	Coefficient estimation
Known mixture	Record	Record	Recovery
Test mixture	Record	Record	Final calculation

Calculations

- A1 = aX1 x CX + aY1 x CY; A2 = aX2 x CX + aY2 x CY
- D = aX1 x aY2 - aY1 x aX2
- CX = (A1 x aY2 - A2 x aY1) / D

• CY = (aX1 x A2 - aX2 x A1) / D

Worked Example

Illustrative coefficients in absorbance per microgram/mL: aX1 = 0.08, aY1 = 0.02, aX2 = 0.01 and aY2 = 0.05. Mixture responses A1 = 0.46 and A2 = 0.20 give D = 0.0038.
CX = (0.46 x 0.05 - 0.20 x 0.02) / 0.0038 = 5.00 micrograms/mL.
CY = (0.08 x 0.20 - 0.01 x 0.46) / 0.0038 = 3.00 micrograms/mL. These are concentrations in the measured dilution.

Result and Interpretation

• Report both contents with the units used for the coefficients and the individual dilution corrections.
• Assess mixture recovery and matrix interference before accepting the mathematical solution.
• Similar spectra may require another wavelength strategy, derivative methods or chromatographic separation.

Precautions

• Use consistent concentration units for both coefficient sets.
• Maintain solvent and pH conditions between standards and mixtures.
• Do not force negative concentrations to zero without investigating the model.
• Confirm the determinant and coefficient order before calculation.

Viva Questions and Answers

What does a small determinant mean?

The two equations contain little independent information, so small measurement errors can greatly affect the solution.

Why test a known mixture?

It checks spectral additivity and the complete calculation under realistic conditions.

Where is dilution applied?

After resolving the concentrations in the measured solution.

Quantitative Analysis by HPLC

Practical 3 - Bench practical

Aim

To separate and quantify an analyte by a suitable HPLC method while evaluating chromatographic performance.

Principle

An analyte distributes between a stationary phase and flowing mobile phase. Retention and separation depend on the column chemistry, mobile-phase composition, flow, temperature and analyte ionisation.

A detector response is related to concentration using a qualified calibration or comparison with a reference preparation. Retention agreement supports identification but needs the selectivity evidence required for the intended use.

Materials and Requirements

- HPLC system with suitable column and detector
- Method-specified mobile phase and diluent
- Reference material, blank and placebo
- Qualified filters, vials and volumetric glassware

Procedure

1. Record the column identity, mobile-phase composition, flow, temperature, detector settings, injection volume and method version.
2. Prepare mobile phase and solutions using compatible grades and the adopted filtration and degassing process. Record solution stability and reference potency.
3. Check the system for leaks and equilibrate using the instrument procedure. Establish a stable baseline before the analytical sequence.
4. Run a blank, reference preparations and system-suitability injections. Evaluate retention, resolution, peak shape and repeatability against predefined method criteria.
5. Inject independently prepared test solutions bracketed by appropriate check standards. Include a blank after high concentrations when carryover is a concern.
6. Review peak identification and integration consistently. Retain the original chromatograms and document any justified integration changes.
7. Calculate concentration or assay, reverse dilutions and review the complete sequence before reporting. Preserve audit-trail and processing information.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Injection	Retention time (min)	Area / area ratio	Resolution or comment
Blank	Record	Record	Interference / carryover
Reference replicates	Record	Record	Suitability
Test preparation 1	Record	Record	Assay

Injection	Retention time (min)	Area / area ratio	Resolution or comment
Test preparation 2	Record	Record	Preparation precision

Calculations

- Resolution, Rs = 2(tR2 - tR1) / (w1 + w2), using baseline peak widths
- Theoretical plates, N = 16(tR / w)^2, using baseline width
- For matched dilutions in a valid external-standard comparison: assay (%) = test area / standard area x reference concentration / nominal test concentration x reference potency (%)

Worked Example

Illustrative adjacent peaks: retention times 5.00 and 5.40 min; baseline widths 0.20 and 0.24 min.

Rs = 2(0.40) / 0.44 = 1.82. The first peak gives N = 16(5.00/0.20)^2 = 10000.

For equal nominal concentrations, test and standard areas of 49000 and 50000 with reference potency 99.7% give assay = 49000/50000 x 99.7 = 97.706%.

These values illustrate calculations; use the adopted method criteria to decide whether a sequence is acceptable.

Result and Interpretation

- Report assay or concentration together with the observed suitability results.
- A resolved, reproducible peak must also be shown to be specific for the intended analysis.
- Investigate failed suitability or carryover before using affected test results.

Precautions

- Use compatible solvents and the column pressure and temperature limits.
- Collect solvent waste in designated containers and keep incompatible wastes separate.
- Prevent particles and bubbles entering the flow path.
- Avoid selective reintegration or reinjection to obtain a preferred result.

Viva Questions and Answers

Why equilibrate the column?

A stable stationary-phase environment improves retention and response reproducibility.

Does a single retention time prove identity?

No; coelution is possible and identity requires the intended method evidence.

Why bracket test injections?

Check standards can reveal response drift during the run.

Analysis by Gas Chromatography

Practical 4 - Bench practical

Aim

To quantify a suitable volatile analyte using gas chromatography and evaluate separation and detector response.

Principle

A vaporised preparation is carried through a temperature-controlled column by a gas stream. Compounds separate according to volatility and interactions with the stationary phase.

Quantification may use an external standard or an internal-standard area ratio. The analyte must be sufficiently volatile and stable for the selected method; derivatisation, where needed, is a separate validated operation.

Materials and Requirements

- Gas chromatograph with the selected detector and column
- Qualified carrier-gas supply and gas-specific leak-check equipment
- Reference analyte and internal standard where specified
- Suitable diluent, crimped vials and calibrated glassware

Procedure

1. Record detector, column, gas identities, flow or pressure mode, inlet mode, temperature program and acquisition settings from the selected method.
2. Confirm instrument readiness and gas-supply checks with the trained operator. Inspect blanks before introducing test material.
3. Prepare standards and test solutions in closed containers, controlling evaporation and using the same internal-standard concentration where applicable.
4. Establish calibration using the intended response or area ratio and verify a separate check preparation.
5. Inject the analytical sequence with blanks and suitable reference checks. Assess retention repeatability, separation and carryover.
6. Review chromatograms for interference and integration consistency. Retain the temperature program and raw data with the report.
7. Calculate the measured concentration, apply dilutions and assess suitability using the method-specific limits.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Preparation	Analyte area	Internal-standard area	Ratio / concentration
Blank	Record	Record	Check interference
Calibrators	Record	Record	Fit relationship
Independent check	Record	Record	Recovery
Test solutions	Record	Record	Final result

Calculations

- Response ratio R = analyte area / internal-standard area

- If R = mC + b, then C = (R - b) / m
- Original concentration = measured concentration x documented dilution factor

Worked Example

Illustrative calibration: R = 2.50C with C in mg/mL. A test ratio of 1.20 gives C = 1.20/2.50 = 0.480 mg/mL. With a 20-fold dilution, the original concentration is 9.60 mg/mL.
A consistent internal-standard amount and acceptable recovery are assumed; the numerical example does not specify a universal GC program.

Result and Interpretation

- Report concentration with the calibration model, dilution and sequence checks.
- Consider evaporative losses and inlet discrimination when recoveries differ between preparations.
- Interpret identity with the specificity available from the detector and method.

Precautions

- Observe instrument-specific precautions for hot inlets, detectors and pressurised gases.
- Hydrogen-containing systems require the prescribed leak checks and shutdown procedure.
- Keep volatile preparations tightly closed.
- Use the appropriate gas regulator and approved exhaust arrangements.

Viva Questions and Answers

Why use an internal standard?

A suitable standard can compensate for some preparation and injection variability.

Can every drug be analysed directly by GC?

No; volatility and thermal stability may limit direct analysis.

Why include blanks after concentrated injections?

They help assess carryover and contamination.

Fluorimetric Estimation of Riboflavin or Quinine

Practical 5 - Bench practical

Aim

To estimate riboflavin or quinine using a calibrated fluorescence response under controlled solution conditions.

Principle

Certain molecules emit light after excitation. Emission depends on analyte concentration, excitation and emission settings, solvent, pH and the chemical environment.

At suitable low concentrations, a calibration can relate fluorescence response to analyte concentration. Quenching, scattering and inner-filter effects can invalidate this simple relationship at higher concentrations.

Materials and Requirements

- Spectrofluorimeter and suitable clean cells
- Riboflavin or quinine reference material
- Method-specified solvent and blank
- Light-protective containers and volumetric glassware

Procedure

1. Record the selected analyte, solvent, pH, excitation and emission settings, slit widths and detector conditions from the adopted method.
2. Prepare a reference stock and dilute to a working series that is sufficiently dilute for a linear response. Protect light-sensitive preparations as required.
3. Scan or verify the reference excitation and emission behaviour before the quantitative run.
4. Measure the blank, calibrators, independent check and test solutions with consistent geometry and timing.
5. Inspect calibration residuals and assess whether dilution restores proportional response in a concentrated test preparation.
6. Calculate the test concentration from the blank-corrected calibration and apply all dilution factors.
7. Record solution age, light exposure and instrument settings so that another analyst can reproduce the measurement.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Preparation	Concentration	Fluorescence response	Blank-corrected response
Blank	0	Record	0 reference
Reference levels	Record	Record	Record
Check preparation	Record	Record	Record
Test dilution	Record	Record	Record

Calculations

- $F_{corrected} = F_{measured} - F_{blank}$

• If F_corrected = mC + b, then C = (F_corrected - b) / m

Worked Example

Illustrative data: blank response 10 units, test response 90 units and calibration F_corrected = 40C.

C = (90 - 10)/40 = 2.00 micrograms/mL in the measured dilution.

A 25-fold dilution gives 50.0 micrograms/mL in the original preparation. Verify that the response lies within the calibrated range.

Result and Interpretation

• Report the concentration and the conditions under which the calibration was established.
• A decrease in response at high concentration can reflect optical or chemical interference rather than less analyte.
• Compare recovery in the relevant matrix before treating the method as suitable for a formulation.

Precautions

• Keep pH, solvent and temperature consistent.
• Avoid fluorescent contamination from detergents or damaged cells.
• Use the selected light-protection conditions.
• Dilute preparations when required instead of extrapolating beyond the working range.

Viva Questions and Answers

What is quenching?

A reduction in fluorescence caused by the molecular environment or interacting species.

Why protect riboflavin solutions?

Light exposure can change the analyte and its response.

Why record slit widths?

They influence signal intensity and spectral resolution.

Metal Estimation by Flame Photometry and AAS

Practical 6 - Practical study

Aim

To compare flame-emission and atomic-absorption measurements for specified metals.

Principle

Flame photometry measures emitted radiation, whereas AAS measures absorption of element-specific radiation. Calibration, matrix effects, atomisation conditions and interferences must be controlled separately for the selected element and technique.

Materials and Requirements

- Approved metal reference, blank and matrix check
- Qualified flame-emission or AAS instrument
- Validated digestion or dilution record and gas-system controls
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Choose the element, wavelength, atomisation system and validated preparation for the actual matrix.
3. Prepare calibration, blank and an independent check; verify background and interference controls.
4. Have trained staff operate the specified instrument and assess calibration and replicate readings.
5. Calculate metal content with all dilution and preparation factors and compare technique selectivity and limitations.
6. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Preparation	Technique / wavelength	Response / concentration	Metal content
Blank	Specify	Measure	Evaluate
Reference check	Specify	Measure	Recovery
Test digest	Specify	Measure	Calculate

Calculations

- Metal content (mg/kg) = concentration (mg/L) x final digest volume (L) x dilution / test mass (kg)

Worked Example

Illustrative digest contains 0.40 mg/L metal in 0.050 L from 0.0020 kg material: content = 10 mg/kg.
This is an arithmetic example; use the actual element-specific specification to assess it.

Result and Interpretation

• State the element, method, blank, recovery and quantitation limits.

Precautions

• Use trained gas and flame operation.
• Prevent metal contamination.
• Do not assume identical matrix effects across elements.

Viva Questions and Answers

What does AAS measure?

Absorption of radiation by atomised analyte species.

Why analyse a blank?

Preparation and reagents may introduce the metal.

Why use a matrix check?

The preparation matrix can change analytical response.

Total Quality Management Case Study

Practical 7 - Quality case-study practical

Aim

To investigate a defined pharmaceutical-quality case and prepare a defensible decision record.

Principle

A quality-system decision connects evidence, patient or product risk, cause assessment, authorised action and effectiveness. A suspected cause is a hypothesis until supported by evidence.

Materials and Requirements

- Fictional case pack, batch history and applicable SOP
- Investigation, risk and action templates
- Trend data and a documented approval pathway
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Construct a factual timeline and distinguish facts from assumptions.
3. Identify affected batches, containment and immediate product-risk questions.
4. Gather relevant laboratory, equipment, personnel and manufacturing evidence and test plausible causes.
5. Propose justified actions with owners, dates and effectiveness measures; record disposition and closure through authorised roles.
6. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Finding / evidence	Risk / impact	Action / owner	Effectiveness evidence
Observed problem	Assess	Assign	Define
Cause hypothesis	Test	Assign	Verify
Product disposition	Justify	Approve	Record

Calculations

- Recurrence rate = repeated events / defined opportunities x 100
- State the observation period and denominator when comparing rates.

Worked Example

Illustrative 6 documentation omissions in 200 records give 3.0%. After an intervention, 1 in 200 gives 0.5%. Review comparable workload and surveillance before attributing improvement to the action.

Case assignment

- Repeated late release and customer complaints

• Map supplier, production, laboratory and customer interfaces; define ownership, feedback and an improvement cycle.
• Track complaint rate and right-first-time release with defined denominators.

Result and Interpretation

• Produce a signed-role investigation summary with evidence, unresolved questions and justified closure criteria.

Precautions

• Do not invent a root cause or delete contrary evidence.
• Distinguish containment from permanent correction.
• Do not use repeated testing to obtain a passing result.

Viva Questions and Answers

What distinguishes correction from corrective action?

Correction addresses the immediate problem; corrective action addresses its cause.

What closes an action effectively?

Evidence that it was implemented and achieved the intended sustained result.

Why assess product impact early?

Containment and disposition may be needed before the investigation is complete.

Six Sigma Case Study

Practical 8 - Quality case-study practical

Aim

To investigate a defined pharmaceutical-quality case and prepare a defensible decision record.

Principle

A quality-system decision connects evidence, patient or product risk, cause assessment, authorised action and effectiveness. A suspected cause is a hypothesis until supported by evidence.

Materials and Requirements

- Fictional case pack, batch history and applicable SOP
- Investigation, risk and action templates
- Trend data and a documented approval pathway
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Construct a factual timeline and distinguish facts from assumptions.
3. Identify affected batches, containment and immediate product-risk questions.
4. Gather relevant laboratory, equipment, personnel and manufacturing evidence and test plausible causes.
5. Propose justified actions with owners, dates and effectiveness measures; record disposition and closure through authorised roles.
6. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Finding / evidence	Risk / impact	Action / owner	Effectiveness evidence
Observed problem	Assess	Assign	Define
Cause hypothesis	Test	Assign	Verify
Product disposition	Justify	Approve	Record

Calculations

- Recurrence rate = repeated events / defined opportunities x 100
- State the observation period and denominator when comparing rates.

Worked Example

Illustrative 6 documentation omissions in 200 records give 3.0%. After an intervention, 1 in 200 gives 0.5%. Review comparable workload and surveillance before attributing improvement to the action.

Case assignment

- Excess tablet-weight variation

• Use Define, Measure, Analyse, Improve and Control; qualify measurement, stratify causes and test an improvement.
• Use a stable-process variation measure; a sigma label without a distribution and opportunity definition is incomplete.

Result and Interpretation

• Produce a signed-role investigation summary with evidence, unresolved questions and justified closure criteria.

Precautions

• Do not invent a root cause or delete contrary evidence.
• Distinguish containment from permanent correction.
• Do not use repeated testing to obtain a passing result.

Viva Questions and Answers

What distinguishes correction from corrective action?

Correction addresses the immediate problem; corrective action addresses its cause.

What closes an action effectively?

Evidence that it was implemented and achieved the intended sustained result.

Why assess product impact early?

Containment and disposition may be needed before the investigation is complete.

Change-Control Case Study

Practical 9 - Quality case-study practical

Aim

To investigate a defined pharmaceutical-quality case and prepare a defensible decision record.

Principle

A quality-system decision connects evidence, patient or product risk, cause assessment, authorised action and effectiveness. A suspected cause is a hypothesis until supported by evidence.

Materials and Requirements

- Fictional case pack, batch history and applicable SOP
- Investigation, risk and action templates
- Trend data and a documented approval pathway
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Construct a factual timeline and distinguish facts from assumptions.
3. Identify affected batches, containment and immediate product-risk questions.
4. Gather relevant laboratory, equipment, personnel and manufacturing evidence and test plausible causes.
5. Propose justified actions with owners, dates and effectiveness measures; record disposition and closure through authorised roles.
6. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Finding / evidence	Risk / impact	Action / owner	Effectiveness evidence
Observed problem	Assess	Assign	Define
Cause hypothesis	Test	Assign	Verify
Product disposition	Justify	Approve	Record

Calculations

- Recurrence rate = repeated events / defined opportunities x 100
- State the observation period and denominator when comparing rates.

Worked Example

Illustrative 6 documentation omissions in 200 records give 3.0%. After an intervention, 1 in 200 gives 0.5%. Review comparable workload and surveillance before attributing improvement to the action.

Case assignment

- Replacement of a granulator impeller

• Record reason, risk, affected documents, qualification and comparability needs before approval and implementation.
• Define effectiveness checks, regulatory impact and closure evidence.

Result and Interpretation

• Produce a signed-role investigation summary with evidence, unresolved questions and justified closure criteria.

Precautions

• Do not invent a root cause or delete contrary evidence.
• Distinguish containment from permanent correction.
• Do not use repeated testing to obtain a passing result.

Viva Questions and Answers

What distinguishes correction from corrective action?

Correction addresses the immediate problem; corrective action addresses its cause.

What closes an action effectively?

Evidence that it was implemented and achieved the intended sustained result.

Why assess product impact early?

Containment and disposition may be needed before the investigation is complete.

Out-of-Specification Investigation

Practical 10 - Quality case-study practical

Aim

To investigate a defined pharmaceutical-quality case and prepare a defensible decision record.

Principle

A quality-system decision connects evidence, patient or product risk, cause assessment, authorised action and effectiveness. A suspected cause is a hypothesis until supported by evidence.

Materials and Requirements

- Fictional case pack, batch history and applicable SOP
- Investigation, risk and action templates
- Trend data and a documented approval pathway
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Construct a factual timeline and distinguish facts from assumptions.
3. Identify affected batches, containment and immediate product-risk questions.
4. Gather relevant laboratory, equipment, personnel and manufacturing evidence and test plausible causes.
5. Propose justified actions with owners, dates and effectiveness measures; record disposition and closure through authorised roles.
6. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Finding / evidence	Risk / impact	Action / owner	Effectiveness evidence
Observed problem	Assess	Assign	Define
Cause hypothesis	Test	Assign	Verify
Product disposition	Justify	Approve	Record

Calculations

- Recurrence rate = repeated events / defined opportunities x 100
- State the observation period and denominator when comparing rates.

Worked Example

Illustrative 6 documentation omissions in 200 records give 3.0%. After an intervention, 1 in 200 gives 0.5%. Review comparable workload and surveillance before attributing improvement to the action.

Case assignment

- Assay result outside the approved specification

• Secure preparations and data, perform a timely laboratory assessment, then extend to manufacturing as warranted.
• A retest requires scientific justification; a passing retest does not erase the original result.

Result and Interpretation

• Produce a signed-role investigation summary with evidence, unresolved questions and justified closure criteria.

Precautions

• Do not invent a root cause or delete contrary evidence.
• Distinguish containment from permanent correction.
• Do not use repeated testing to obtain a passing result.

Viva Questions and Answers

What distinguishes correction from corrective action?

Correction addresses the immediate problem; corrective action addresses its cause.

What closes an action effectively?

Evidence that it was implemented and achieved the intended sustained result.

Why assess product impact early?

Containment and disposition may be needed before the investigation is complete.

Out-of-Trend Investigation

Practical 11 - Quality case-study practical

Aim

To investigate a defined pharmaceutical-quality case and prepare a defensible decision record.

Principle

A quality-system decision connects evidence, patient or product risk, cause assessment, authorised action and effectiveness. A suspected cause is a hypothesis until supported by evidence.

Materials and Requirements

- Fictional case pack, batch history and applicable SOP
- Investigation, risk and action templates
- Trend data and a documented approval pathway
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Construct a factual timeline and distinguish facts from assumptions.
3. Identify affected batches, containment and immediate product-risk questions.
4. Gather relevant laboratory, equipment, personnel and manufacturing evidence and test plausible causes.
5. Propose justified actions with owners, dates and effectiveness measures; record disposition and closure through authorised roles.
6. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Finding / evidence	Risk / impact	Action / owner	Effectiveness evidence
Observed problem	Assess	Assign	Define
Cause hypothesis	Test	Assign	Verify
Product disposition	Justify	Approve	Record

Calculations

- Recurrence rate = repeated events / defined opportunities x 100
- State the observation period and denominator when comparing rates.

Worked Example

Illustrative 6 documentation omissions in 200 records give 3.0%. After an intervention, 1 in 200 gives 0.5%. Review comparable workload and surveillance before attributing improvement to the action.

Case assignment

- Assay remains within specification but falls outside an established trend
- Confirm the trend rule, review stability and method/process history and evaluate product impact.

• Separate a statistical signal from a confirmed cause; maintain monitoring and justified action.

Result and Interpretation

• Produce a signed-role investigation summary with evidence, unresolved questions and justified closure criteria.

Precautions

• Do not invent a root cause or delete contrary evidence.
• Distinguish containment from permanent correction.
• Do not use repeated testing to obtain a passing result.

Viva Questions and Answers

What distinguishes correction from corrective action?

Correction addresses the immediate problem; corrective action addresses its cause.

What closes an action effectively?

Evidence that it was implemented and achieved the intended sustained result.

Why assess product impact early?

Containment and disposition may be needed before the investigation is complete.

Corrective and Preventive Action Case Study

Practical 12 - Quality case-study practical

Aim

To investigate a defined pharmaceutical-quality case and prepare a defensible decision record.

Principle

A quality-system decision connects evidence, patient or product risk, cause assessment, authorised action and effectiveness. A suspected cause is a hypothesis until supported by evidence.

Materials and Requirements

- Fictional case pack, batch history and applicable SOP
- Investigation, risk and action templates
- Trend data and a documented approval pathway
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Construct a factual timeline and distinguish facts from assumptions.
3. Identify affected batches, containment and immediate product-risk questions.
4. Gather relevant laboratory, equipment, personnel and manufacturing evidence and test plausible causes.
5. Propose justified actions with owners, dates and effectiveness measures; record disposition and closure through authorised roles.
6. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Finding / evidence	Risk / impact	Action / owner	Effectiveness evidence
Observed problem	Assess	Assign	Define
Cause hypothesis	Test	Assign	Verify
Product disposition	Justify	Approve	Record

Calculations

- Recurrence rate = repeated events / defined opportunities x 100
- State the observation period and denominator when comparing rates.

Worked Example

Illustrative 6 documentation omissions in 200 records give 3.0%. After an intervention, 1 in 200 gives 0.5%. Review comparable workload and surveillance before attributing improvement to the action.

Case assignment

- Recurring line-clearance documentation omissions

• Define the problem and product impact, investigate causes, assign corrective and preventive actions with owners.
• Verify implementation and effectiveness against a preselected recurrence measure.

Result and Interpretation

• Produce a signed-role investigation summary with evidence, unresolved questions and justified closure criteria.

Precautions

• Do not invent a root cause or delete contrary evidence.
• Distinguish containment from permanent correction.
• Do not use repeated testing to obtain a passing result.

Viva Questions and Answers

What distinguishes correction from corrective action?

Correction addresses the immediate problem; corrective action addresses its cause.

What closes an action effectively?

Evidence that it was implemented and achieved the intended sustained result.

Why assess product impact early?

Containment and disposition may be needed before the investigation is complete.

Deviation Investigation

Practical 13 - Quality case-study practical

Aim

To investigate a defined pharmaceutical-quality case and prepare a defensible decision record.

Principle

A quality-system decision connects evidence, patient or product risk, cause assessment, authorised action and effectiveness. A suspected cause is a hypothesis until supported by evidence.

Materials and Requirements

- Fictional case pack, batch history and applicable SOP
- Investigation, risk and action templates
- Trend data and a documented approval pathway
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Construct a factual timeline and distinguish facts from assumptions.
3. Identify affected batches, containment and immediate product-risk questions.
4. Gather relevant laboratory, equipment, personnel and manufacturing evidence and test plausible causes.
5. Propose justified actions with owners, dates and effectiveness measures; record disposition and closure through authorised roles.
6. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Finding / evidence	Risk / impact	Action / owner	Effectiveness evidence
Observed problem	Assess	Assign	Define
Cause hypothesis	Test	Assign	Verify
Product disposition	Justify	Approve	Record

Calculations

- Recurrence rate = repeated events / defined opportunities x 100
- State the observation period and denominator when comparing rates.

Worked Example

Illustrative 6 documentation omissions in 200 records give 3.0%. After an intervention, 1 in 200 gives 0.5%. Review comparable workload and surveillance before attributing improvement to the action.

Case assignment

- Unplanned mixing-time departure

• Contain affected material, record actual chronology, assess process and product risk and investigate the cause.
• Assign disposition through authorised quality review and track necessary actions.

Result and Interpretation

• Produce a signed-role investigation summary with evidence, unresolved questions and justified closure criteria.

Precautions

• Do not invent a root cause or delete contrary evidence.
• Distinguish containment from permanent correction.
• Do not use repeated testing to obtain a passing result.

Viva Questions and Answers

What distinguishes correction from corrective action?

Correction addresses the immediate problem; corrective action addresses its cause.

What closes an action effectively?

Evidence that it was implemented and achieved the intended sustained result.

Why assess product impact early?

Containment and disposition may be needed before the investigation is complete.

Stability Study Protocol

Practical 14 - Protocol-writing practical

Aim

To draft an executable, product-specific stability study protocol.

Principle

Stability assesses time-dependent chemical, physical, microbiological and performance attributes in the proposed container system. Accelerated conditions support an assessment but do not by themselves establish a universal expiry period.

Materials and Requirements

- Approved stability protocol and product-specific specifications
- Qualified chamber records and container details
- Stability-indicating assay, impurity and physical-test data
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Define batches, pack orientation, storage conditions, intervals, tests and statistical plan in the protocol.
3. Verify chamber qualification and retain actual monitoring, excursions and sample-pull records.
4. Review content, degradants, physical attributes and performance at each interval using qualified methods.
5. Plot each relevant attribute against time; investigate atypical results without deleting them and assess the supported storage period.
6. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Interval / batch	Actual storage condition	Assay / degradants	Physical / performance result
Initial	Record	Record	Record
Intermediate	Record	Record	Record
Final available point	Record	Record	Record

Calculations

- For a justified first-order model: ln(Ct/C0) = -kt; t90 = -ln(0.90)/k
- Do not extrapolate a shelf life without the applicable stability and statistical justification.

Worked Example

Illustrative first-order k = 0.0020 month^-1 gives t90 = 52.7 months mathematically.

This is a model calculation, not a product expiry claim. Real assignment requires the complete attribute, packaging and stability evidence.

Protocol deliverable

• Include scope, responsibilities, batch selection, pack, storage rationale, pull schedule, test methods, criteria, chamber controls, excursion handling, data review and approval.
• Prepare a sample-accountability table and distinguish long-term, accelerated, intermediate and in-use studies where applicable.

Result and Interpretation

• Report the actual data period, trends, excursions and limits of any extrapolation.

Precautions

• Use product- and market-appropriate conditions rather than a universal chamber schedule.
• Keep container and sampling traceability.
• Do not estimate shelf life from assay alone.

Viva Questions and Answers

What is stability indicating?

The method can distinguish the intended analyte from relevant degradation and matrix effects.

Why study the marketed pack?

The pack can influence moisture, light and gas exposure.

Can one accelerated result prove expiry?

A justified programme and complete evidence are required.

Process Capability Analysis

Practical 15 - Practical study

Aim

To calculate and interpret process capability only after assessing statistical stability.

Principle

Cp compares a specification width with six within-process standard deviations. Cpk also accounts for off-centring. Capability indices can mislead when the process is unstable, the measurement system is unsuitable or distribution assumptions fail.

Materials and Requirements

- Time-ordered process dataset and subgroup rationale
- Approved upper and lower specification limits
- Control-chart and statistical software or worksheet
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Check measurement-system suitability, subgroup formation and data completeness.
3. Plot a suitable control chart and investigate special-cause evidence before capability estimation.
4. Estimate within-process variation using the justified method and assess distributional assumptions.
5. Compute Cp and Cpk and distinguish them from indices based on overall variation; discuss centring and uncertainty.
6. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Statistic	Input	Calculation	Interpretation
Specification limits	LSL / USL	Width	Record
Within variation	Sigma estimate	6 sigma	Record
Centre	Mean	Cpk	Record

Calculations

- Cp = (USL - LSL)/(6 sigma_within)
- Cpk = min[(USL - mean)/(3 sigma_within), (mean - LSL)/(3 sigma_within)]

Worked Example

Illustrative LSL = 95, USL = 105, mean = 101, sigma_within = 1.0. Cp = 10/6 = 1.67; Cpk = min(4/3,6/3) = 1.33. These calculations assume a stable process and an appropriate variation model; they do not supply a universal approval threshold.

Result and Interpretation

• Report the control-chart conclusion, estimation method and confidence or data limitations with the indices.

Precautions

• Do not confuse control limits with specifications.
• Retain time order.
• Do not remove inconvenient observations to inflate capability.

Viva Questions and Answers

Why can Cpk be lower than Cp?

The process mean is off-centre.

What are control limits?

Limits derived from process behaviour, distinct from product specifications.

Can an unstable process have a useful single capability claim?

Stability must first be assessed and special causes addressed.

In-Process and Finished-Product Quality Control

Practical 16 - QC record practical

Aim

To prepare and interpret an in-process and finished-product quality-control panel.

Principle

In-process tests support manufacturing control; release tests assess the finished product against approved specifications. The required panel depends on dosage form, route, product and current monograph or dossier.

Materials and Requirements

- Model tablet, capsule, oral liquid and sterile-product specifications
- Supplied manufacturing and laboratory results
- Controlled sampling, test and release templates
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Map each quality attribute to its manufacturing stage, sampling plan, method and limit.
3. For tablets and capsules review mass, content, uniformity and applicable disintegration or dissolution evidence.
4. For oral liquids review identity, content, pH, delivered volume, physical uniformity and microbial controls; for sterile products add the relevant sterility, endotoxin, particulate and integrity requirements.
5. Reconcile individual results, deviations and analytical suitability before preparing a quality disposition recommendation.
6. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Dosage form / stage	Attribute / method	Result and limit	Decision / follow-up
Tablet / capsule	Specify panel	Enter	Evaluate
Oral liquid	Specify panel	Enter	Evaluate
Sterile product	Specify panel	Enter	Evaluate

Calculations

- Percentage deviation = (observed - target)/target x 100
- A numerical average cannot substitute for a required individual-unit criterion.

Worked Example

Illustrative target tablet mass 400 mg and observed mean 404 mg differ by +1.0%.

The mass calculation does not establish content uniformity or a passing release decision; apply the separate product tests.

Result and Interpretation

• Present the full quality panel and identify any missing or unacceptable evidence.

Precautions

• Use current product-specific criteria.
• Do not infer sterility from appearance.
• Keep sampling and batch traceability.

Viva Questions and Answers

Is mass uniformity the same as content uniformity?

No; drug distribution and composition also matter.

Why test during processing?

It can identify variation before the batch is finished.

Who releases a batch?

The authorised quality function under the applicable system.

Assay of Raw Materials Against Monographs

Practical 17 - Analytical practical

Aim

To plan and document the official assay and identification evidence required for a raw material.

Principle

A titration relates analyte amount to the amount of standard reagent required by a defined reaction. Reaction stoichiometry, endpoint selection, blank consumption and reagent standardisation determine the calculation. The test preparation, blank, calibration or titrant standardisation and independent controls are part of the measurement. State the actual concentration units, test conditions and adopted method before interpreting the result.

Materials and Requirements

- Selected official compound and adopted monograph
- Appropriate standardised titrant and primary-standard record
- Endpoint indicator or potentiometric system
- Qualified balance and volumetric equipment
- Controlled method and raw-data worksheet

Procedure

1. Identify the material, intended attribute, method version and acceptance criteria. Record preparation and instrument or reagent identities.
2. Prepare the prescribed blank and reference or standardised reagent. Verify the measurement with an independent check where applicable.
3. Prepare a representative weighed test portion in the specified solvent. Ensure the reaction conditions and dissolution are appropriate.
4. Titrate using the defined endpoint, recording initial and final burette readings and a reagent blank.
5. Repeat on independent portions and calculate the content using the reaction stoichiometry and the actual titrant concentration.
6. Record individual readings for independently prepared test portions. Keep all raw observations, including unsuccessful measurements and their investigation.
7. Calculate the result on the stated mass, volume or area basis, including dilution, blank and recovery corrections as justified.
8. Compare the evidence with the applicable criteria and write a conclusion limited to the tested preparation and conditions.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Preparation / attribute	Method condition	Raw measurement	Calculated result
Titrant standardisation	Record	Record	Calculate
Blank	Record	Record	Calculate
Test portion 1	Record	Record	Calculate

Preparation / attribute	Method condition	Raw measurement	Calculated result
Test portion 2	Record	Record	Calculate

Calculations

• Analyte amount (mol) = blank-corrected titrant volume (L) x actual titrant molarity x stoichiometric ratio
• Assay (%) = measured analyte mass / weighed preparation mass x 100

Worked Example

Illustrative 1:1 reaction: corrected titrant volume 10.00 mL, molarity 0.1000 mol/L and analyte molar mass 180.16 g/mol.

Measured analyte = 0.01000 x 0.1000 x 180.16 = 0.18016 g.

For a 0.1820 g test portion, assay = 98.99% approximately. This example does not assign the reaction to a particular official drug.

Monograph-to-record mapping

• Identify the current applicable monograph, material grade and any water, solvent or purity correction.
• Map identity, assay and impurity requirements to method records and raw data. A supplier certificate supports the record but does not replace required receipt testing.

Result and Interpretation

• State the endpoint and stoichiometric basis, including whether water or other correction factors are required by the monograph.
• Report replicate variability and the evidence that the method can measure the intended attribute in this matrix.

Precautions

• Use the actual standardised reagent concentration.
• Avoid endpoint overshoot and parallax.
• Select a blank with the same reagent and solvent conditions.
• Use the adopted laboratory procedure, suitable controls and the designated waste arrangements.

Viva Questions and Answers

Why standardise a titrant?

Its actual concentration can differ from the nominal preparation.

Why is stoichiometry essential?

The reagent-to-analyte mole relationship determines the mass calculation.

Why correct for the blank?

Other components may consume titrant.

Related and Foreign Substances

Practical 18 - Bench practical

Aim

To assess related or foreign substances in a drug or raw material using the applicable official method.

Principle

An analyte distributes between a stationary phase and flowing mobile phase. Retention and separation depend on the column chemistry, mobile-phase composition, flow, temperature and analyte ionisation.

A detector response is related to concentration using a qualified calibration or comparison with a reference preparation. Retention agreement supports identification but needs the selectivity evidence required for the intended use.

Materials and Requirements

- HPLC system with suitable column and detector
- Method-specified mobile phase and diluent
- Reference material, blank and placebo
- Qualified filters, vials and volumetric glassware

Procedure

1. Record the column identity, mobile-phase composition, flow, temperature, detector settings, injection volume and method version.
2. Prepare mobile phase and solutions using compatible grades and the adopted filtration and degassing process. Record solution stability and reference potency.
3. Check the system for leaks and equilibrate using the instrument procedure. Establish a stable baseline before the analytical sequence.
4. Run a blank, reference preparations and system-suitability injections. Evaluate retention, resolution, peak shape and repeatability against predefined method criteria.
5. Inject independently prepared test solutions bracketed by appropriate check standards. Include a blank after high concentrations when carryover is a concern.
6. Review peak identification and integration consistently. Retain the original chromatograms and document any justified integration changes.
7. Calculate concentration or assay, reverse dilutions and review the complete sequence before reporting. Preserve audit-trail and processing information.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Injection	Retention time (min)	Area / area ratio	Resolution or comment
Blank	Record	Record	Interference / carryover
Reference replicates	Record	Record	Suitability
Test preparation 1	Record	Record	Assay
Test preparation 2	Record	Record	Preparation precision

Calculations

• Resolution, Rs = 2(tR2 - tR1) / (w1 + w2), using baseline peak widths
• Theoretical plates, N = 16(tR / w)^2, using baseline width
• For matched dilutions in a valid external-standard comparison: assay (%) = test area / standard area x reference concentration / nominal test concentration x reference potency (%)

Worked Example

Illustrative adjacent peaks: retention times 5.00 and 5.40 min; baseline widths 0.20 and 0.24 min.
Rs = 2(0.40) / 0.44 = 1.82. The first peak gives N = 16(5.00/0.20)^2 = 10000.
For equal nominal concentrations, test and standard areas of 49000 and 50000 with reference potency 99.7% give assay = 49000/50000 x 99.7 = 97.706%.
These values illustrate calculations; use the adopted method criteria to decide whether a sequence is acceptable.

Impurity reporting

• Record identification, reporting and quantitation requirements from the adopted method and product context.
• Use appropriate impurity reference materials or justified response factors. Equal peak areas need not represent equal masses.
• Assess blank, placebo, carryover, resolution, quantitation capability and relevant forced-degradation evidence. Do not label every additional peak as a drug degradant without investigation.

Result and Interpretation

• Report assay or concentration together with the observed suitability results.
• A resolved, reproducible peak must also be shown to be specific for the intended analysis.
• Investigate failed suitability or carryover before using affected test results.

Precautions

• Use compatible solvents and the column pressure and temperature limits.
• Collect solvent waste in designated containers and keep incompatible wastes separate.
• Prevent particles and bubbles entering the flow path.
• Avoid selective reintegration or reinjection to obtain a preferred result.

Viva Questions and Answers

Why equilibrate the column?

A stable stationary-phase environment improves retention and response reproducibility.

Does a single retention time prove identity?

No; coelution is possible and identity requires the intended method evidence.

Why bracket test injections?

Check standards can reveal response drift during the run.

Preformulation Studies for Tablets

Practical 19 - Bench practical

Aim

To characterise a drug and its compatibility with the intended dosage form before formulation development.

Principle

Preformulation connects material properties to manufacturing and performance risks. Relevant attributes include identity, solid state, solubility, ionisation, particle characteristics, stability and compatibility.

The investigation is driven by the intended route and dosage form. Oral solid development may emphasise flow and compactability, whereas a parenteral concept also requires consideration of aqueous behaviour, route-compatible excipients and sterile-product development.

Materials and Requirements

- Identified drug and candidate excipients
- Suitable solubility, thermal, spectroscopic and particle-characterisation methods
- Calibrated balances and controlled-condition containers
- Material and experimental-design records

Procedure

1. Define the intended dosage form, target product attributes and the questions the study must answer.
2. Review identity and available material information, then select tests that address actual development risks.
3. Determine equilibrium solubility under defined conditions and examine pH dependence when scientifically appropriate.
4. Assess particle size, morphology, flow or compaction behaviour for solid-dose development. Record the measurement method and limitations.
5. Compare the drug, individual excipients and selected mixtures by suitable methods such as FTIR and DSC, supported by relevant storage studies.
6. Prepare a risk matrix linking each result to a formulation or process decision. Identify experiments needed to resolve uncertainty.
7. Write the preformulation report with raw data, material grades, conditions and the rationale for the selected development approach.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Attribute	Method and conditions	Result	Development implication
Identity / solid state	Record	Record	Assess
Solubility / pH	Record	Record	Assess
Particle / flow attributes	Record	Record	Assess
Compatibility / stability	Record	Record	Assess

Calculations

• Solubility = dissolved analyte mass / equilibrated liquid volume
• Recovery (%) = recovered measured amount / expected amount x 100

Worked Example

Illustrative equilibrium determination: 12.0 mg analyte is measured in 10.0 mL equilibrated supernatant after correcting the assay dilution.

Solubility = 1.20 mg/mL under the recorded pH and temperature.

A second condition giving 3.60 mg/mL shows a three-fold analytical difference. Stability and material-state changes must be checked before assigning the change solely to improved solubilisation.

Result and Interpretation

• Summarise the development risks and the evidence for the chosen formulation strategy.
• Spectral or thermal changes are investigated in context; a single shifted peak is not sufficient proof of incompatibility.
• Identify the conditions for which the results apply.

Precautions

• Avoid confusing kinetic dissolution with equilibrium solubility.
• Control temperature, equilibration and separation conditions.
• Assess analyte loss to filters or containers.
• Evaluate material and excipient grades relevant to the intended product.

Viva Questions and Answers

Why study preformulation?

It identifies material-related risks before committing to a formulation or process.

Does an FTIR change always prove a chemical reaction?

No; physical interactions and measurement conditions can also alter spectra.

Why specify dosage form?

Different routes and manufacturing processes require different material attributes.

Preformulation Studies for Parenteral Products

Practical 20 - Bench practical

Aim

To characterise a drug and its compatibility with the intended dosage form before formulation development.

Principle

Preformulation connects material properties to manufacturing and performance risks. Relevant attributes include identity, solid state, solubility, ionisation, particle characteristics, stability and compatibility.

The investigation is driven by the intended route and dosage form. Oral solid development may emphasise flow and compactability, whereas a parenteral concept also requires consideration of aqueous behaviour, route-compatible excipients and sterile-product development.

Materials and Requirements

- Identified drug and candidate excipients
- Suitable solubility, thermal, spectroscopic and particle-characterisation methods
- Calibrated balances and controlled-condition containers
- Material and experimental-design records

Procedure

1. Define the intended dosage form, target product attributes and the questions the study must answer.
2. Review identity and available material information, then select tests that address actual development risks.
3. Determine equilibrium solubility under defined conditions and examine pH dependence when scientifically appropriate.
4. Assess particle size, morphology, flow or compaction behaviour for solid-dose development. Record the measurement method and limitations.
5. Compare the drug, individual excipients and selected mixtures by suitable methods such as FTIR and DSC, supported by relevant storage studies.
6. Prepare a risk matrix linking each result to a formulation or process decision. Identify experiments needed to resolve uncertainty.
7. Write the preformulation report with raw data, material grades, conditions and the rationale for the selected development approach.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Attribute	Method and conditions	Result	Development implication
Identity / solid state	Record	Record	Assess
Solubility / pH	Record	Record	Assess
Particle / flow attributes	Record	Record	Assess
Compatibility / stability	Record	Record	Assess

Calculations

• Solubility = dissolved analyte mass / equilibrated liquid volume
• Recovery (%) = recovered measured amount / expected amount x 100

Worked Example

Illustrative equilibrium determination: 12.0 mg analyte is measured in 10.0 mL equilibrated supernatant after correcting the assay dilution.

Solubility = 1.20 mg/mL under the recorded pH and temperature.

A second condition giving 3.60 mg/mL shows a three-fold analytical difference. Stability and material-state changes must be checked before assigning the change solely to improved solubilisation.

Result and Interpretation

• Summarise the development risks and the evidence for the chosen formulation strategy.
• Spectral or thermal changes are investigated in context; a single shifted peak is not sufficient proof of incompatibility.
• Identify the conditions for which the results apply.

Precautions

• Avoid confusing kinetic dissolution with equilibrium solubility.
• Control temperature, equilibration and separation conditions.
• Assess analyte loss to filters or containers.
• Evaluate material and excipient grades relevant to the intended product.

Viva Questions and Answers

Why study preformulation?

It identifies material-related risks before committing to a formulation or process.

Does an FTIR change always prove a chemical reaction?

No; physical interactions and measurement conditions can also alter spectra.

Why specify dosage form?

Different routes and manufacturing processes require different material attributes.

Effect of pH on Drug Solubility

Practical 21 - Practical study

Aim

To construct and interpret a pH-solubility profile for a selected ionisable compound.

Principle

For an ideal monoprotic weak acid S = S0(1 + 10^(pH - pKa)); for a weak base S = S0(1 + 10^(pKa - pH)). These equations assume the appropriate solid phase and equilibrium; salts, complexes and degradation can cause deviations.

Materials and Requirements

- Selected weak acid or base and defined buffer series
- Calibrated pH meter and temperature-controlled equilibration
- Validated concentration assay and phase-separation method
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Choose a justified pH range and document buffer composition and ionic strength.
3. Equilibrate excess solid at each pH, recording actual pH before and after equilibration.
4. Separate particles without disturbing the equilibrium and assay intact drug with appropriate blanks.
5. Plot solubility against pH and compare the observations with the ionisation model and possible solid-phase changes.
6. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Buffer / actual pH	Temperature / time	Measured solubility	Model prediction
Below pKa	Record	Record mg/mL	Calculate
Near pKa	Record	Record mg/mL	Calculate
Above pKa	Record	Record mg/mL	Calculate

Calculations

- Weak acid: S/S0 = 1 + 10^(pH - pKa)
- Weak base: S/S0 = 1 + 10^(pKa - pH)

Worked Example

Illustrative weak acid: S0 = 0.010 mg/mL and pKa = 4.0. At pH 5.0, predicted S = 0.110 mg/mL.
The prediction is conditional; compare it with measured intact-drug content and final pH.

Result and Interpretation

• Report the observed profile and limitations rather than assigning an ideal curve as experimental evidence.

Precautions

• Recheck pH after adding drug.
• Assess chemical stability and filter recovery.
• Do not extend the simple equation to multiprotic systems without a suitable model.

Viva Questions and Answers

What is S0?

Intrinsic solubility of the un-ionised form under the defined conditions.

Why measure final pH?

Drug addition or equilibration can shift pH.

Why can data depart from the equation?

Solid-phase changes, nonideality, complexation or degradation may occur.

Primary and Secondary Packaging Quality Control

Practical 22 - Practical study

Aim

To evaluate primary and secondary packaging against their intended protection, compatibility and information functions.

Principle

Primary packaging contacts or directly contains the product; secondary packaging supports protection, identification and distribution. Material identity, container-closure integrity and compatibility are distinct attributes.

Materials and Requirements

- Approved packaging specification and model components
- Dimension, seal, barrier or integrity data as applicable
- Label, artwork, reconciliation and transport records
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Identify packaging material, supplier, component revision and intended product use.
3. Assess the specified appearance, dimensions, closure fit and mechanical properties using qualified methods.
4. Review required barrier, leak or container-closure integrity evidence and compatibility including extractables/leachables assessment where relevant.
5. Check label legibility, batch and expiry fields, storage text, coding and issued/used/rejected component reconciliation.
6. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Component / lot	Attribute and method	Result / criterion	Disposition
Primary container	Identity / dimensions	Enter	Assess
Closure / seal	Integrity test	Enter	Assess
Secondary carton	Artwork / coding	Enter	Assess

Calculations

- Unreconciled components = issued - (used + rejected + returned), using mutually exclusive documented categories

Worked Example

Illustrative 1,000 labels issued, 960 used, 25 rejected and 15 returned give zero unreconciled labels. Zero discrepancy does not establish that the artwork was correct; both checks are needed.

Result and Interpretation

- Report each component result and the evidence supporting the product-pack system.

Precautions

- Use nonoverlapping reconciliation categories.
- Do not substitute a visual check for a validated integrity method.
- Control artwork revisions.

Viva Questions and Answers

Why assess compatibility?

The product and pack can interact during storage.

What is a secondary pack?

An outer packaging level such as a carton.

Why reconcile labels?

It helps control mix-ups and unexplained component use.

Accelerated Stability Study

Practical 23 - Practical study

Aim

To evaluate long-term or accelerated stability data and prepare a justified stability conclusion.

Principle

Stability assesses time-dependent chemical, physical, microbiological and performance attributes in the proposed container system. Accelerated conditions support an assessment but do not by themselves establish a universal expiry period.

Materials and Requirements

- Approved stability protocol and product-specific specifications
- Qualified chamber records and container details
- Stability-indicating assay, impurity and physical-test data
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Define batches, pack orientation, storage conditions, intervals, tests and statistical plan in the protocol.
3. Verify chamber qualification and retain actual monitoring, excursions and sample-pull records.
4. Review content, degradants, physical attributes and performance at each interval using qualified methods.
5. Plot each relevant attribute against time; investigate atypical results without deleting them and assess the supported storage period.
6. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Interval / batch	Actual storage condition	Assay / degradants	Physical / performance result
Initial	Record	Record	Record
Intermediate	Record	Record	Record
Final available point	Record	Record	Record

Calculations

- For a justified first-order model: ln(Ct/C0) = -kt; t90 = -ln(0.90)/k
- Do not extrapolate a shelf life without the applicable stability and statistical justification.

Worked Example

Illustrative first-order k = 0.0020 month^-1 gives t90 = 52.7 months mathematically.

This is a model calculation, not a product expiry claim. Real assignment requires the complete attribute, packaging and stability evidence.

Result and Interpretation

• Report the actual data period, trends, excursions and limits of any extrapolation.

Precautions

• Use product- and market-appropriate conditions rather than a universal chamber schedule.
• Keep container and sampling traceability.
• Do not estimate shelf life from assay alone.

Viva Questions and Answers

What is stability indicating?

The method can distinguish the intended analyte from relevant degradation and matrix effects.

Why study the marketed pack?

The pack can influence moisture, light and gas exposure.

Can one accelerated result prove expiry?

A justified programme and complete evidence are required.

Solubility Improvement with Surfactants

Practical 24 - Practical study

Aim

To measure the influence of surfactant concentration on apparent equilibrium solubility.

Principle

Micelles and other surfactant assemblies can increase apparent drug solubility. The change depends on surfactant identity, concentration, medium and temperature; an analytical signal must distinguish dissolved material from suspended particles.

Materials and Requirements

- Model drug and approved surfactant levels including zero
- Controlled equilibration and phase-separation equipment
- Matrix-matched assay, blanks and recovery check
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Prepare matched media with fixed pH and temperature, varying only surfactant concentration.
3. Equilibrate excess solid by the adopted method and confirm equilibration with time-point evidence.
4. Separate undissolved particles using a method checked for drug loss or micelle disruption.
5. Assay the clarified phases with matching blanks and compare solubility against surfactant concentration.
6. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Surfactant level	Equilibration time	Drug concentration	Relative solubility
Zero	Record	Record mg/mL	Baseline
Low	Record	Record mg/mL	Calculate
High	Record	Record mg/mL	Calculate

Calculations

- Solubility enhancement ratio = apparent solubility in test medium / solubility in matched surfactant-free medium

Worked Example

Illustrative concentrations 0.020 and 0.120 mg/mL give a sixfold enhancement.

This does not prove that unbound drug concentration or absorption increases sixfold.

Result and Interpretation

• Plot the measured concentrations and describe uncertainty, equilibration evidence and filtration controls.

Precautions

• Control pH and temperature.
• Use matrix-matched calibration when surfactant affects response.
• Do not treat a cloudy dispersion as a true dissolved phase.

Viva Questions and Answers

Why use excess solid?

A persistent solid phase helps establish saturation.

What is apparent solubility?

The method-measured dissolved amount, potentially including micelle-associated drug.

Does solubilisation prove bioavailability?

Further release, permeability and in-vivo evidence is needed.

Solubility Improvement by Co-Solvency

Practical 25 - Practical study

Aim

To determine how a selected cosolvent changes equilibrium solubility.

Principle

Changing solvent composition changes solvent-solute interactions. An empirical log-linear model may fit part of a composition range, but it is not a universal law and does not establish route-specific suitability.

Materials and Requirements

- Model drug, water and approved cosolvent
- Composition records and controlled equilibration
- Matrix-matched assay and separation controls
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Prepare a series with explicitly stated mass or volume fractions; account for mixing contraction when relevant.
3. Equilibrate excess drug in each composition at the same temperature.
4. Separate the solid phase, verify recovery and assay with standards prepared in compatible matrices.
5. Plot log solubility versus cosolvent fraction and discuss the supported range and potential precipitation on dilution.
6. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Cosolvent fraction	Equilibration condition	Solubility	Log solubility
0.00	Record	Record	Calculate
0.20	Record	Record	Calculate
0.40	Record	Record	Calculate

Calculations

- Empirical fit: log10 S = log10 S_water + sigma x cosolvent fraction

Worked Example

Illustrative S_water = 0.010 mg/mL and sigma = 3.0. At fraction 0.20, predicted S = 0.010 x 10^0.6 = 0.0398 mg/mL.

Verify the model with measured data; do not assume the formulation remains soluble after dilution.

Result and Interpretation

• Report composition basis, fit limitations and dilution behaviour.

Precautions

• Use approved solvent handling and waste controls.
• Keep temperature constant.
• Assess volatility and actual mixture composition.

Viva Questions and Answers

Why specify fraction basis?

Mass and volume fractions differ.

What does sigma describe?

An empirical sensitivity of log solubility to cosolvent fraction.

What can happen on dilution?

Loss of solvent capacity can cause precipitation.

Determination of pKa and Log P

Practical 26 - Practical study

Aim

To estimate pKa and partition behaviour using appropriate experimental data.

Principle

pKa describes ionisation equilibrium. Log P describes partitioning of the neutral species between defined phases; log D includes all species at a specified pH. These quantities cannot be used interchangeably.

Materials and Requirements

- Selected ionisable compound and titration or spectroscopic dataset
- Pre-equilibrated octanol and aqueous phases or supplied partition data
- Qualified pH and concentration measurements
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Determine pKa from a justified titration or spectroscopic method, with temperature and ionic-strength records.
3. For partitioning, define phases and pH, check stability and avoid emulsions.
4. Measure equilibrated concentrations in both phases and check material balance and phase-volume changes.
5. Calculate the stated partition or distribution coefficient and distinguish its ionisation basis.
6. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Measurement	pH / condition	Raw value	Calculated parameter
pKa experiment	Record	Record titration / spectral data	Estimate pKa
Aqueous phase	Record pH	Concentration	Enter
Organic phase	Record condition	Concentration	Enter

Calculations

- Log P = log10(C_neutral,octanol / C_neutral,water)
- Log D at pH x = log10(C_total,octanol / C_total,water) at pH x

Worked Example

Illustrative neutral-species concentrations 2.0 and 0.020 mg/mL give P = 100 and log P = 2.00.

A total-concentration ratio at a specified pH should generally be reported as D, not automatically P.

Result and Interpretation

• State method, temperature, pH and model assumptions for every reported parameter.

Precautions

• Avoid emulsions and phase cross-contamination.
• Check analytical recovery in both matrices.
• Use the correct logarithm and concentration basis.

Viva Questions and Answers

What distinguishes log D?

It includes the species present at a stated pH.

What happens at pH = pKa for an ideal monoprotic acid?

Ionised and un-ionised concentrations are equal.

Why check mass balance?

Loss or degradation can bias the phase ratio.

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