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Infliximab as a Targeted TNF-A Inhibitor: Pharmaceutical Development for Psoriatic Treatment

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ABSTRACT

Psoriasis is a clinically heterogeneous lifelong skin disease that presents in multiple forms such as plaque, flexural, guttate, pustular or erythrodermic. An estimated 60 million people have psoriasis worldwide, with 1.52% of the general population affected in the UK. An immune-mediated inflammatory disease, psoriasis has a major genetic component. Its association with psoriatic arthritis and increased rates of cardiometabolic, hepatic and psychological comorbidity requires a holistic and multidisciplinary care approach. Psoriasis treatments include topical agents (vitamin D analogues and corticosteroids), phototherapy (narrowband ultraviolet B radiation (NB-UVB) and psoralen and ultraviolet A radiation (PUVA)), standard systemic (methotrexate, ciclosporin and acitretin), biologic (tumour necrosis factor (TNF), interleukin (IL)-17 and IL-23 inhibitors) or small molecule inhibitor (dimethyl fumarate and apremilast) therapies. Advances in the understanding of its pathophysiology have led to development of highly effective and targeted treatments.

KEY WORD: PSORIASIS, ANTIPSORIASTIC DRUGS, INFLIXIMAB

PSORIASIS

INTRODUCTION:

Psoriasis is a chronic proliferative and inflammatory condition of the skin. It is characterized by erythematous plaques covered with silvery scales, particularly over the extensor surfaces, scalp, and lumbosacral region.

The disorder can also affect the joints and eyes. Psoriasis has no cure and the disease waxes and wanes with flareups. Many patients with psoriasis develop depression as the quality of life is poor. There are several subtypes of psoriasis but the plaque type is the most common and presents on the trunk, extremities, and scalp (see Image. Psoriasis, Bilaterally on the Lower Leg). Close examination of the plaques usually reveals white silvery scales.

The eye is involved in about 10% of patients, mostly women. In general, the eye is rarely

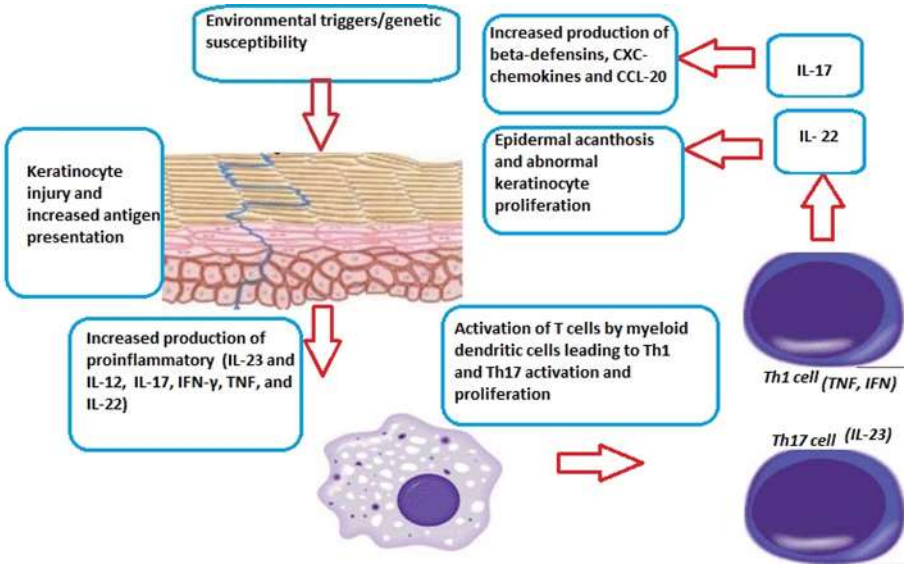
ETIOLOGY

Psoriasis has a prevalence ranging from 0.2% to 4.8%. The exact etiology is unknown, but it is considered to be an autoimmune disease mediated by T lymphocytes. There is an association of HLA antigens seen in many psoriatic patients, particularly in various racial and ethnic groups. Familial occurrence suggests its genetic predisposition. Injury in the form of mechanical, chemical, and radiational trauma induces lesions of psoriasis. Certain drugs like chloroquine, lithium, beta-blockers, steroids, and NSAIDs can worsen psoriasis. Generally, summer improves psoriasis while winter aggravates it. Apart from the above factor's infections, psychological stress, alcohol, smoking, obesity, and hypocalcaemia are other triggering factors for psoriasis.

PATHOPHYSIOLOGY

SIGNS AND SYMPTOMS

- **Skin rashes or patches:** These may start as small bumps and turn into larger patches that are red, dark pink, or purple and covered in loose, silver, white, or tricolored scales. These scaly areas are called plaques. In severe cases, the plaques grow and merge into one another, covering large areas. You are most likely to find them on your scalp, elbows, knees, or lower back.
- **Itchy, painful skin:** The inflamed skin may crack or bleed, especially if you scratch it. That can lead to infection and, in severe cases, cause severe pain, swelling, and fever.



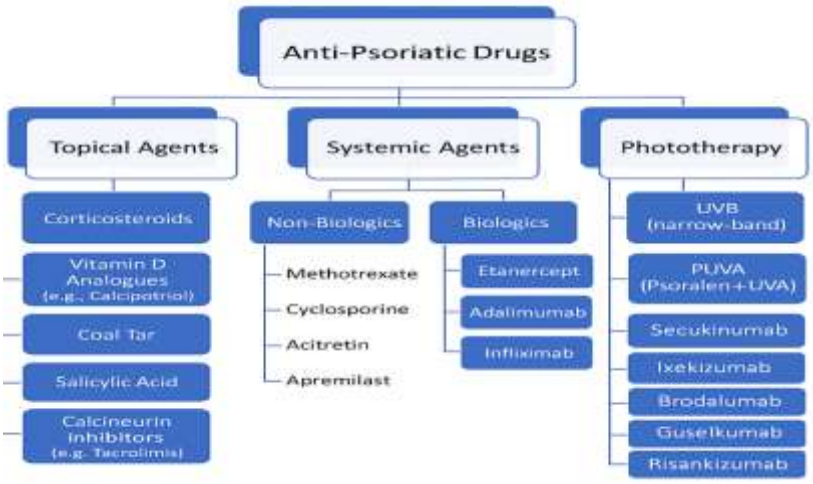
pathophysiology of psoriasis

- **Problems with your fingernails and toenails:** They might change colour and get pits. The nails may also begin to crumble or detach from the nail bed. About half of people with plaque psoriasis have nail trouble.

ANTIPSORIATIC DRUGS

Anti-psoriatic drugs, also known as anti-psoriasis agents, are substances or treatments designed to alleviate or treat the symptoms of psoriasis. They target the abnormal cell growth and inflammation associated with the condition.

Anti-psoriatic refers to substances or treatments that are used to alleviate or treat the symptoms of psoriasis, a skin condition characterized by raised, red, scaly patches. These substances can be natural or synthetic and work by targeting specific mechanisms involved in the development of psoriasis.



CLASSIFICATION OF ANTIPSORIATIC DRUGS

TNF INHIBITORS

- TNF inhibitors work by binding to TNF, preventing it from interacting with its receptors on cells, which would normally trigger an inflammatory response. By blocking TNF, these drugs reduce inflammation throughout the body.

INFLIXIMAB

- Infliximab is a medication, specifically a chimeric monoclonal antibody, primarily used to treat several autoimmune diseases. Infliximab inhibits TNF-α, a signaling protein involved in inflammation, thus reducing the symptoms of autoimmune diseases**.**

- Infliximab is biologically engineered from human and mouse antibody molecules. It works by directly binding to tumour necrosis factor (TNF) in the blood and diseased tissue. Infliximab-bound TNF cannot bind to or activate TNF receptors, which are involved in the development of psoriatic plaques.
- infliximab is an effective treatment for chronic plaque psoriasis with 90% of patients becoming clear or having minimal disease activity after 5 mg/kg infused at weeks 0, 2 and 6. Thereafter, maintenance infusions at approximately 8-weekly intervals may encourage prolonged efficacy.

MECHANISM OF ACTION

1. Binding:

Infliximab binds to TNF-α molecules in the plasma and within the affected skin.

2. Neutralization:

The binding prevents TNF-α from interacting with its receptors, thus neutralizing its activity.

3. Inflammatory Cascade Inhibition:

By blocking TNF-α, infliximab disrupts the inflammatory cascade

that contributes to the development of psoriatic lesions.

4. Cellular Effects:

Infliximab may also trigger apoptosis (programmed cell death) in

TNF-α-producing cells, further reducing the levels of this inflammatory protein.

AVAILABLE OF INFLIXIMAB IN MARKET

BRANDS: Remicade, Infimab, Inflixerel, Tremfiya, etc

REMICADE INJECTION:

Brand: REMICADE

Origin: The origin of this product is Europe

Manufacturer: Janssen Biotech

Active substances: INFLIXIMAB

Strength: 100mg

Pack size: 1 x 100mg Vial

Other known names: Other Known Names REMICADE 100mg

Accessories: Accessories Package insert.

INFIMAB INJECTION:

Brand	Infimab
Manufacturer	sun pharma
Shelf Life	24 Months
Usage/Application	Psoriasis
Packaging Size	1ml
Packaging Type	Vial

PREFORMULATION STUDIES

PARENTRAL DOSAGE FORM: INJECTION

- Preformulation is a group of studies that focus on the physicochemical properties of a new drug candidate that could affect the drug performance and the development of a dosage form.
- Preformulation studies focus on understanding the physicochemical properties of the drug molecule. This includes assessing how the drug behaves under various environmental conditions, such as different pH levels, temperature, and humidity, which are essential for predicting the drug's shelf life and stability.

OBJECTIVES OF PREFORMULATION STUDIES

- Establish the necessary physicochemical parameters of a new drug substance.
- Determine drug kinetic rate profile.
- Develop a stability indicating assay.
- Establish drug compatibility with common excipients.

➢ The goal of these Preformulation studies is to:

- Provide a foundation for developing a stable and safe injectable formulation of infliximab.
- Optimize the formulation to ensure the drug maintains its potency and safety throughout its shelf life.
- Inform formulation decisions, such as excipient selection, formulation design, and manufacturing processes

PREFORMULATION STUDIES FOR INFLIXIMAB INJECTION

Preformulation Studies of Infliximab involve a comprehensive analysis of the physicochemical and biological characteristics of the drug to guide the development of a stable, safe, and effective formulation. Infliximab is a chimeric monoclonal antibody (IgG1) that targets tumour necrosis factor-alpha (TNF-α), used primarily in the treatment of autoimmune diseases like rheumatoid arthritis and Crohn's disease.

1. PHYSICOCHEMICAL CHARACTERISATION

- **Molecular Weight and Structure**:
  - Approx. 149 kDa.
  - Composed of human constant and murine variable regions.

➢ **Molecular Weight Determination**

- **Technique**: SDS-PAGE and MALDI-TOF MS.
- **Procedure**:
  1. Prepare infliximab sample under reducing and non-reducing conditions.
  2. Run SDS-PAGE gel.
  3. Stain gel with Coomassie Blue.
  4. Compare band pattern with known molecular weight markers.
  5. For precise weight: perform MALDI-TOF MS analysis.
- **Isoelectric Point (pI)**:
  - Typically, around pH 6.1–8.5, depending on the glycosylation pattern.

- **Technique**: Isoelectric focusing (IEF) or Capillary Isoelectric Focusing (cIEF).
- **Procedure**:
  1. Prepare protein sample in ampholyte solution.
  2. Load on an IEF gel or cIEF cartridge.
  3. Run voltage gradient to separate based on pI.
  4. Analyse pI using standards or software (in cIEF).
- **Solubility**:

- Soluble in aqueous buffers; solubility can vary with pH and ionic strength.
- Solubility studies help determine suitable pH and buffer systems.

Procedure:

1. Prepare buffer solutions of varying pH (3.0 to 9.0).
2. Dissolve infliximab in each buffer at a fixed concentration (e.g., 1 mg/mL).
3. Incubate at 25°C for 24 h.
4. Centrifuge to remove precipitates.
5. Measure soluble protein concentration via UV spectroscopy at 280 nm.

- **Hydrophobicity and Charge Distribution**:
  - Assessed using techniques like hydrophobic interaction chromatography (HIC) and ion exchange chromatography (IEX).
- **Glycosylation Profile**:
  - Important for bioactivity, stability, and immunogenicity Characterized using HPLC, mass spectrometry, and capillary electrophoresis.

2. Stability Studies

- **Thermal Stability**:
  - Evaluated using Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA).
  - Helps in identifying degradation pathways and optimal storage conditions.

- **Technique**: Differential Scanning Calorimetry (DSC).
- **Procedure**:
  - Prepare infliximab solution (~1 mg/mL) in formulation buffer.
  - Load into DSC instrument.
  - Scan from 10°C to 100°C at 1°C/min.
  - Record melting temperatures (Tm) of domains.

- **pH Stability**:
  - Studied across a pH range to find optimal conditions that prevent aggregation and degradation.
  - **Procedure**:
    - Prepare infliximab solutions in various buffers (pH 3–9).
    - Incubate samples at 25°C and 40°C.
    - Analyse at 0, 7, 14, 28 days:
      - Appearance (colour, clarity)
      - SEC for aggregation
      - SDS-PAGE for degradation
      - ELISA for activity

- **Photostability**:
  - Light sensitivity requires protection during storage and handling.
- **Procedure**:
  - Expose infliximab samples in clear vials to ICH-recommended light conditions:
    - ≥1.2 million lux hours and ≥200 Wh/m² UV.
  - Compare with dark controls.

- Evaluate for:
  - Aggregation (SEC)
  - Activity (ELISA)
  - Chemical degradation (MS).

- **Oxidation and Deamidation**:
  - Common degradation pathways in proteins.
  - Identified using mass spectrometry and peptide mapping.

Oxidation:

- Treat with 0.03% H_2O_2 for 1–3 hours.

Deamidation:

- Incubate in pH 9.0 buffer at 37°C.

Analysis:

- Peptide mapping (LC-MS/MS)
- Functional assay (TNF-α binding ELISA)

1. **Aggregation and Particulate Formation**

Protein aggregation is a critical concern.

Techniques:

- Size-exclusion chromatography (SEC)
- Dynamic light scattering (DLS)
- Analytical ultracentrifugation

- Aim: minimize aggregates, which can lead to immunogenic responses.
- **Technique**: SEC-HPLC and DLS.
- **Procedure (SEC)**:
  - Inject infliximab (0.5–2 mg/mL) into an analytical SEC column.
  - Use isocratic mobile phase (e.g., phosphate-buffered saline).
  - Monitor UV absorbance at 280 nm.
  - Analyse monomer, dimer, and HMW species.

2. **Formulation Excipient Compatibility**

- Common excipients: polysorbate 80, sucrose, sodium phosphate, histidine.
- Compatibility and stabilization assessed under accelerated stress conditions.
- Interaction with surfactants and preservatives is critical to prevent denaturation and aggregation.

Procedure:

- Prepare infliximab formulations with various excipients (e.g., sucrose, trehalose, polysorbate 80, mannitol).
- Subject samples to:
  - Freeze-thaw cycles
  - Accelerated temperatures (25°C, 40°C)
  - Light stress
- Monitor for:
  - Appearance

- pH
- Aggregation
- Potency (ELISA)

3. Biological Activity

- Bioassays (e.g., cell-based assays) to confirm binding to TNF-α remains intact.
- ELISA and Surface Plasmon Resonance (SPR) to assess binding kinetics.
- **Technique**: TNF-α Neutralization Bioassay.

Procedure:

- Culture TNF-α-responsive cell line (e.g., L929).
- Incubate with TNF-α and varying concentrations of infliximab.
- Measure cell viability using MTT or XTT assay.
- Plot dose-response curve to determine EC50.

4. Lyophilization Studies

- Infliximab is often marketed as a lyophilized powder.
- Preformulation includes:
  - Selection of cryo/lyoprotectants (e.g., trehalose, sucrose)
  - Optimization of freeze-drying cycle
  - Reconstitution behaviour and stability post-reconstitution.
- **Procedure**:
  - Prepare formulations with cryoprotectants (sucrose, trehalose).
  - Load into lyophilized.
  - Use thermal analysis (DSC, freeze-drying microscopy) to determine:
    - Freezing point
    - Collapse temperature
  - Optimize primary and secondary drying.
  - Check cake appearance, reconstitution time, and stability post-lyophilization.

5. Container-Closure System Compatibility

- Compatibility with glass vials, rubber stoppers, and plastic syringes.
- Concerns: adsorption, leachable, and extractables.

Procedure:

- Fill infliximab into intended packaging (glass vials, prefilled syringes).
- Store under ICH conditions (25°C/60% RH, 40°C/75% RH).
- Assess:
  - Leachable and extractables (GC-MS, LC-MS)
  - pH drift
  - Particulate matter
  - Potency and aggregation.

6. Analytical Method Development

- Development and validation of methods for:

- Identity (SDS-PAGE, Western blot)
- Purity and heterogeneity (SEC, IEX)
- Potency (bioassays)
- Stability (forced degradation studies.

PARAMETER	DETAILS
SOLUBILITY RECONSTITUTION SOLVENT	Soluble in aqueous buffers, sterile water. Sterile water for injection.
MOLECULAR FORMULA	$C_{6428}H_{9912}N_{1694}O_{1987}S_{46}$
MOLECULAR WEIGHT	~149 kDa
pH RANGE (for formulation)	5.2 – 7.2
ISOELECTRIC POINT	~7.4
STABILITY (pH SENSITIVITY)	Stable at pH 5–6.5; degradation increases outside this range
THERMAL STABILITY	Sensitive to high temperatures; requires refrigeration (2–8°C)
LIGHT STABILITY	Sensitive; store protected from light
DEGRADATION PATHWAYS	Aggregation, deamidation, oxidation
EXCIPIENT COMPATIBILITY	Compatible with sucrose, polysorbate 80, phosphate buffers (FTIR).
EXCIPIENT SENSITIVITY	Sensitive to surfactant type and concentration
RECOMMENDED STORAGE	Lyophilized: 2–8°C; Reconstituted: Use within recommended time under refrigeration.
ANALYTICAL TECHNIQUES	TLC, HPLC, DSC, etc

FORMULATION OF INFLIXIMAB INJECTION

1. **Production of Infliximab (Active Pharmaceutical Ingredient - API)**
   - **Cell development:** Special lab cells are designed to produce Infliximab;

a monoclonal antibody. These cells are stored in freezers as a master stock.

   - **Cell Culture**: Infliximab, a chimeric monoclonal antibody targeting tumor necrosis factor-alpha (TNF-α), is produced using recombinant DNA technology in Chinese Hamster Ovary (CHO) cells. The cells are cultured in bioreactors under controlled conditions to express the antibody.
   - **Harvesting**: After sufficient growth, the cell culture is harvested to collect the supernatant containing the antibody.
2. **Purification of Infliximab**
   - **Chromatography**: The harvested product undergoes multiple purification steps, including Protein A affinity chromatography, ion-exchange chromatography, and size-exclusion chromatography, to isolate infliximab and remove impurities.
   - **Filtration**: Further filtration steps ensure the removal of any remaining particulates or contaminants.
3. **Formulation Preparation**
   - **Buffer Composition**: The purified infliximab is formulated with specific excipients to enhance stability:
     - Sucrose (5%) as a stabilizer
     - Polysorbate 80 (0.005%) as a surfactant
     - Sodium phosphate monobasic and dibasic to maintain pH at approximately 7.2

Concentration Adjustment: The final concentration is adjusted to 10 mg/mL.

INGREDIENTS	QUANTITY
Infliximab	100 mg per vial
Sucrose	500 mg
Polysorbate 80	0.5 mg
Sodium Phosphate Buffer	2.2 mg
Water for Injection	10 mL Sterile Water for Injection, per 100 mg infliximab vial
Dibasic sodium phosphate dihydrate (if needed)	6.1 mg

4. **Sterile Filtration**
    - The formulated solution is passed through a 0.22-micron filter to ensure sterility before filling.
5. **Aseptic Filling and Lyophilization**
    - **Filling**: Under aseptic conditions, the sterile solution is filled into vials.
    - **Lyophilization (Freeze-Drying)**: The filled vials undergo lyophilization to remove water content, resulting in a stable, white lyophilized powder. This process enhances the shelf-life of the product.
6. **Sealing and Packaging**
    - **Sealing**: Post-lyophilization, vials are sealed under vacuum or inert gas (e.g. Nitrogen) to prevent moisture ingress.
    - **Labelling and Packaging**: Vials are labelled with product information and packaged for distribution.
7. **Quality Control Testing**
    - **Sterility Testing**: Ensures the absence of microbial contamination.
    - **Potency Assay**: Confirms the biological activity of infliximab.
    - **Physicochemical Analysis**: Assesses parameters like pH, osmolality, and protein concentration.
    - **Stability Studies**: Evaluate the product's shelf-life under various storage conditions.
8. **Storage and Distribution**
    - **Storage**: Finished products are stored at 2–8°C to maintain stability.
    - **Distribution**: Products are distributed under cold chain logistics to healthcare facilities.

EVALUATION OF INFLIXIMAB INJECTION

Evaluating the quality and safety of infliximab injection involves stringent testing to ensure its sterility, absence of pyrogens, clarity, isotonicity, and uniformity of content.

1. Sterility Testing

Objective: Ensure the absence of viable microorganisms in the product.

Methods:

- **Membrane Filtration Method:** Filter a known volume of the sample through a membrane filter, then transfer the filter to a suitable culture medium. Incubate at 30–35°C for 14 days.

Procedure:

- **Membrane Filtration Method:**

1. Filter a specified volume (e.g., 100 mL or as per product volume) of the infliximab solution through a sterilized membrane filter (0.45 µm pore size).
2. Transfer the membrane filter aseptically into two types of culture media:
    - Fluid Thioglycolate Medium (FTM) for anaerobic and aerobic bacteria.
    - Soybean-Casein Digest Medium (SCDM) for fungi.

3. Incubate FTM tubes at 30–35°C for 14 days.
4. Incubate SCDM tubes at 20–25°C for 14 days.
5. Observe for any microbial growth (turbidity, colour change).
6. No growth indicates sterility.

- **Direct Inoculation Method:** Inoculate a known volume of the sample directly into suitable culture media. Incubate at 30–35°C for 14 days.

Procedure:

- Aseptically inoculate a specified volume of the infliximab solution into culture media (FTM and SCDM).
- Incubate similarly as above.
- Observe for microbial growth.

2. Pyrogen Testing

Objective: Detect pyrogens that can induce fever upon administration.

Methods:

- **Rabbit Pyrogen Test (RPT):** Inject the test sample into rabbits and monitor their body temperature for a specified period. A significant rise in temperature indicates the presence of pyrogens.

Procedure:

1. Inject a specific volume of infliximab into three healthy rabbits intravenously.
2. Monitor rectal temperatures at 0, 30, 60, 90, and 120 minutes post-injection.
3. If the total rise in temperature of any rabbit exceeds 0.6°C (or the sum of three rabbits is over 1.4°C), the test is positive for pyrogens.

- **Limulus Amoebocyte Lysate (LAL) Test:** Utilize the blood cells of the horseshoe crab, which react with endotoxins to form a gel. The presence of endotoxins in the sample causes this gelation.

Procedure:

1.Prepare serial dilutions of the infliximab sample.

2.Add LAL reagent to the sample in endotoxin-free tubes.

3.Incubate at 37°C for 60 minutes.

4.Check for gel formation indicating endotoxin presence.

5.Quantify endotoxin concentration using a standard curve.

3. Clarity and Particulate Matter Testing

Objective: Ensure the solution is free from visible particles and is clear.

Methods:

- **Visual Inspection:** Hold the container against a white background with suitable illumination. Rotate to detect any visible particles.

Procedure:

1. Inspect the injection solution against a white and black background under bright, diffuse light.
2. Rotate and tilt the container to detect any floating or settled particles.
3. The solution should appear clear and free of visible particles.

- **Particulate Matter Testing (USP <788>):**
  1. Use an automated particle counter to measure particles ≥10 μm and ≥25 μm in size.
  2. The particle counts must meet USP limits for injections.
- **Nephelometric Method:** Use a nephelometer to measure the turbidity of the solution, which correlates with particulate matter.

4.Isotonicity Testing

Objective: Ensure the solution has an osmotic pressure similar to that of blood to prevent haemolysis or tissue irritation.

Methods:

Cryoscopic Method: Measure the freezing point depression of the solution and compare it to that of an isotonic solution

Procedure:

- **Freezing Point Depression Method:**
    1. Measure the freezing point of the infliximab solution using a cryoscope.
    2. Compare with the freezing point of normal saline (0.9% NaCl).
    3. The freezing point should be close to −0.52°C (isotonic).
- **Sodium Equivalent Method:** Calculate the sodium chloride equivalent of the solution based on its freezing point depression.

Procedure:

1. Calculate NaCl equivalent based on solution composition.
2. Adjust formulation if necessary to maintain isotonicity.

5.Uniformity of Content

Objective: Ensure uniform distribution of the active ingredient within each dosage unit.

Methods:

- **High-Performance Liquid Chromatography (HPLC):** Analyse individual units to determine the amount of active ingredient.
- **Content Uniformity Test:** Select a specified number of units and determine if the amount of active ingredient in each is within the acceptable range.

Procedure:

- **Sample Preparation:**
    1. Reconstitute or dilute the injection vial as per the label instructions.
- **Assay by HPLC or ELISA:**
    1. Prepare a calibration curve with known concentrations of infliximab.
    2. Analyse individual samples using reversed-phase HPLC or a validated ELISA method.
    3. Calculate the drug content.
    4. Ensure each unit is within ±10% of the label claim.

6.Leak testing

Leak testing is done to ensure the integrity of product and prevent contamination.

Methods:

- **Vacuum decay method:**

Procedure:

1. creating vacuum around sealed package.
2. Measure the rate of vacuum decay.
3. Rapid decay indicates a leak.

- **High voltage leak detection:**

- Non-destructive method.
- Uses high voltage to detect leaks in parenteral products.

- **Dye immersion test:**

Packages are submerged in dye solution. Leaks are identified by dye penetration and staining.

- **Vacuum leak tester:**

1.placing the package inside chamber.

2.close chamber lid. creating vacuum.

3.observing if sample maintain shape and no dye penetration observed – no leak.

6. Additional Tests (Specific to Biologics)

- **Potency Assay:** Using cell-based bioassays to confirm the biological activity of infliximab.

procedure:

1. Culture cells sensitive to TNF-α cytotoxicity.
2. Incubate cells with a fixed concentration of TNF-α.
3. Add serial dilutions of infliximab to wells.
4. Incubate for required time period.
5. Measure cell viability or TNF-α neutralization.
6. Compare results to reference standard to calculate relative potency.

- **Immunogenicity Testing:** Assessment of anti-drug antibodies in clinical samples.
- **Stability Studies:** Evaluate physical and chemical stability under recommended storage conditions over time.

procedure:

1. Store infliximab vials at recommended conditions (usually 2–8°C).
2. At predetermined intervals (0, 3, 6, 12 months), sample vials.
3. Test for sterility, potency, clarity, particulate matter, and physical appearance.
4. Verify all parameters meet specifications.
5. Document findings to support shelf life claims.

PACKAGING, STORAGE AND LABELLING OF INFLIXIMAB INJECTION

LABEL:

Must include the following;

- Brand name
- Content name
- Composition
- Dosage form
- Dose
- Route of administration
- Storage
- Usage, indication
- Warning, precautions
- Mfg no., batch no
- Mfg date, exp date
- Manufacturer name.

PACKAGING:

Primary container: glass vial

Secondary container: carton

STORAGE: Store unopened vials in a refrigerator at 2°C to 8°C (36°F to 46°F). at room temperature at 30°C up to 6 months.

- After reconstitution use within 3 hours.
- Once removed from cold storage cannot be returned to it.
- Light protection is essential.

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