WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Methotrexate Unveiled: A Pharmaceutic Perspective in Psoriasis Therapy

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ABSTRACT

Psoriasis is a skin disease that lasts a lifetime and can seem different on various people. It might appear as plaque, flexural, guttate, pustular, or erythrodermic. Psoriasis affects about 60 million individuals around the world, and in the UK, 1.52% of the population has it. Psoriasis is an autoimmune inflammatory disease that runs in families. It necessitates a holistic and multidisciplinary approach to treatment because it is connected to psoriatic arthritis and increased risks of cardiometabolic, hepatic, and mental comorbidities. It is established that methotrexate is safe and works to treat psoriasis and rheumatoid arthritis. There haven't been any randomized controlled trials that prove it works for psoriatic arthritis, but it has been used to treat it anyhow. The biggest randomized trial so far did not support its use as a disease-modifying medication, although observational studies have backed its role. Current treatment guidelines state it can be used as a first-line medication to treat psoriatic arthritis, especially when it predominantly affects the joints in the hands and feet. The first "treat-to-target" research in psoriatic arthritis looked at tight control versus normal care. It concluded that methotrexate worked effectively as a single dose in the first 12 weeks. Over the course of 12 weeks, this experiment revealed that methotrexate helped by making peripheral arthritis, skin and nail disease, enthesitis, and dactylitis better.

KEY WORDS: Psoriasis, Methotrexate, Immunosuppressant, Inflammation, Preformulation Studies, Tablet Formulation, Compatibility Studies, Stability Studies

INTRODUCTION TO PSORIASIS

What is psoriasis? It is a skin disease that causes a rash with itchy, scaly areas, most often on the knees, elbows, trunk, and scalp. Psoriasis is a common, long-lasting (chronic) illness that has no cure. It can hurt, hinder you from sleeping, and make it hard to pay attention. The disease usually goes through cycles, getting worse for a few weeks or months and then getting better for a period. People who are genetically likely to have psoriasis generally get it from infections, cuts, burns, and some medicines. You can get aid with your symptoms with some therapies. You can also improve your life by changing your behaviors and finding solutions to deal with psoriasis.

SYMPTOMS

A rash that is patchy and looks extremely different on different people. It can range from small spots of scaling that look like dandruff to huge eruptions all over the body. Rashes that are diverse hues, such purple with gray scale on brown or black skin and pink or red with silver scale on white skin. Little scaling patches are common in kids. Skin that is dry, cracked, and may bleed, and itches, burns, or hurts. Rashes that come and go in cycles and last for a few weeks or months.

METHOTREXATE

Methotrexate is a drug that decreases the activity of the immune system. This helps reduce the pain and swelling that accompany with inflammation. It is often the first thing doctors try to treat psoriatic arthritis. Methotrexate helps cure PsA in a number of ways, such as:

- Assisting tissue repair: Methotrexate helps white blood cells mend tissues that have been injured, which helps them heal.
- Increasing adenosine production: The Arthritis Foundation adds that methotrexate causes cells release adenosine, which is a chemical that prevents things that promote inflammation.
- Slowing down the production of cytokines: Slowing down the production of cytokines, which are substances that cause swelling. others with PsA frequently have more cytokines in their joints than others who don't have it. A study from 2003 shows that methotrexate might help inhibit the body from producing cytokines.

MECHANISM OF ACTION

When folylpolyglutamate penetrates into tissues, it turns methotrexate into a methotrexate polyglutamate. Methotrexate stops enzymes from making nucleotides. Some of these enzymes are dihydrofolate reductase, thymidylate synthase, aminoimidazole carboxamide ribonucleotide transformylase (AICART), and amido phosphoribosyltransferase. 1 Cells can't divide if you stop making nucleotides.

In https://www.mcafee.com/content/dam/npcld/ecommerce/japac/NGM/en-apac-ngm-post-exp-blast78.jpg In those with rheumatoid arthritis, methotrexate polyglutamates stop AICART more than methotrexate does. 1 This block makes . A report on AICART ribonucleotide, which. This prevents adenosine deaminase, which makes adenosine triphosphate and adenosine pile up outside of cells. This turns on adenosine receptors, which prevents inflammation.

PREFORMULATION STUDIES OF METHOTREXATE TABLET

Preformulation studies are a crucial early phase in pharmaceutical development where the physical and chemical properties of a new drug substance are characterized to aid in the development of a safe, stable, and effective dosage form. These studies aim to understand how these properties influence the drug's performance and suitability for formulation.

CLASSIFICATION OF PREFORMULATION STUDIES OF METHOTREXATE

1. Organoleptic properties
2. Physicochemical properties
3. Micromeritic study
4. Compatibility study

1. ORGANOLEPTIC PROPERTY

Methotrexate tablets are typically off-white, cream yellow, or tan colored. They have a characteristic taste that is often described as bitter or bland, and they are generally considered to be odourless.

2. PHYSICOCHEMICAL PROPERTY

PARTICLE SIZE

Particle size of a tablet is the measurement of the diameter or dimensions of the constituent powder or granule particles used in the tablet formulation before compression.

MELTING POINT

Melting point is defined as the temperature at which a solid substance changes into a liquid under atmospheric pressure. At this temperature, the solid and liquid phases of the substance coexist in equilibrium. It is a characteristic physical property of a pure substance and is commonly used to assess purity—impurities typically lower and broaden the melting point range.

PH

pH is defined as the measure of the hydrogen ion concentration [H+] [H^+] [H+] in a solution. It indicates how acidic or basic (alkaline) a solution

SOLUBILITY

Solubility is the maximum amount of a substance (solute) that can dissolve in a given quantity of solvent at a specified temperature and pressure, forming a homogeneous solution.

MOISTURE CONTENT

Moisture content refers to the amount of water present in a substance, typically expressed as a percentage of the total weight or mass.

UV ABSORPTION

UV absorption is the process by which a substance absorbs ultraviolet (UV) light, typically in the wavelength range of 200–400 nanometres. This occurs when the electrons in a molecule absorb energy from UV light and become excited, moving from a lower energy level (ground state) to a higher energy level (excited state).

3. MICROMERITIC PROPERTY

ANGLE OF REPOSE

Angle of repose is the maximum angle at which a pile of granular material (like a powder) remains stable without sliding. It reflects the flowability or cohesiveness of the material.

Angle of Repose (θ)=tan−1(h/r)

BULK DENSITY

Bulk density is defined as the mass of a powder divided by the total volume it occupies, including the volume of the particles themselves and the void spaces (air) between particles.

TAP DENSITY

Tap density is the density of a powder after it has been mechanically tapped or vibrated in a container to allow particles to settle and occupy minimum volume.

CARRS INDEX

Carr's Index is a measure of the flowability and compressibility of a powder, specifically the difference between the bulk density and tap density of the powder. It provides insight into how easily a powder can be compacted and its potential for poor flow.

4. COMPATIBILTY STUDIES

A compatibility study is an investigation conducted to assess the chemical, physical, and microbiological compatibility of a drug (or active pharmaceutical ingredient, API) with excipients (inactive ingredients such as binders, fillers, stabilizers, solvents) and other components in a formulation, including packaging materials.

This study aims to identify any potential interactions, such as degradation, precipitation, colour changes, or incompatibilities that could affect the safety, efficacy, or stability of the drug product. Compatibility studies are crucial to ensure that the final formulation remains effective, safe, and stable throughout its shelf life.

STABILITY STUDIES

A stability study is conducted to evaluate how the chemical, physical, and microbiological properties of methotrexate change over time under different environmental conditions (e.g., temperature, humidity, light). The goal is to determine the shelf life, appropriate storage conditions, and expiration date of methotrexate formulations.

PREFORMULATION ASPECT	DETAIL OF CONSIDERATION
ACTIVE PHARMACEUTICAL INGREDIENT	METHOTREXATE(CHEMICAL NAME :4-AMINO-10-METHYLFOLIC ACID)
COLOR ODOR TASTE	YELLOW TO ORANGE CRYSTALLINE POWDER ODORLESS TASTELESS
MOLECULAR FORMULA	$C_{20}H_{22}N_8O_5$
MOLECULAR WEIGHT	454.45g/mol
PARTICLE SIZE	FINE POWDER(MICRONIZED IF NEEDED FOR IMPROVED DISSOLUTION)
MELTING POINT	162-165^0 C
PKa	4.9(APPROX) –ACIDIC NATURE,MAY AFFECT FORMULATION AND RELEASE PROFILE
SOLUBILITY	SPARINGLY SOLUBLE IN WATER,INSOLUBLE IN ETHANOL,CHLOROFORM
pH	7 – 9 (STABLE IN NEUTRAL TO SLIGHTLY ALKALINE CONDITION)

STABILITY	SENSITIVE TO LIGHT,HEAT,MOISTURE.MUST BE STORED IN DRY,COOL,DARK PLACE
COMPATIBILITY	IT IS WITH COMMON EXCIPIENT SUCH AS LACTOSE ,MICROCRYSTALLINECELLULOSE,STARCH AND MAGNESIUM STEARATE
EXCIPIENTS	FILLERS:LACTOSE, MICROCRYSTALLINE CELLULOSE
	DISINTEGRANTS:STARCH,SODIUM STARCH GLYCOLATE
	LUBRICANTS:MAGNESIUM STEARATE
	GLIDANTS:COLLOIDAL SILICON DIOXIDE TALC
	BINDERS:PVP(POLY VINYL PYRROLIDONE) HPMC (HYDROXYPROPYL METHYLCELLULOSE)
TABLET FORMULATION CONSIDERATION	COATING MIGHT BE REQUIRED FOR STABILITY. TABLET HARDNESS MUST BE OPTIMIZED TO ENSURE MECHANICAL INTEGRITY
DISSOLUTION	IT HAS SLOW DISSOLUTION RATE DUE TO LOW SOLUBILITY

FORMULATION STUDIES OF METHOTREXATE TABLET

1. MATERIAL PREPARATION

Ingredients:

- Methotrexate Sodium (API)
- Lactose Monohydrate (Diluent)
- Microcrystalline Cellulose (Binder/Diluent)
- Sodium Starch Glycolate (Disintegrant)
- PVP K30 (Binder)
- Isopropyl Alcohol or Water (Granulating agent)
- Talc (Glidant)
- Magnesium Stearate (Lubricant)

All materials should be passed through appropriate mesh sieves (commonly #60) before use.

2. MIXING / BLENDING

- Step 1: Accurately weigh Methotrexate sodium and other intragranular ingredients (e.g., lactose, MCC, disintegrant).
- Step 2: Mix the dry powders uniformly in a blender for 10–15 minutes to ensure homogeneity.

3. WET GRANULATION

- Step 3: Prepare binder solution by dissolving PVP K30 in isopropyl alcohol (or water).
- Step 4: Slowly add the binder solution to the dry mix while continuously mixing to form a damp, cohesive mass.
- Step 5: Pass the wet mass through a #12 or #16 mesh sieve to form granules.

4. DRYING

- Step 6: Dry the granules in a tray dryer or fluid bed dryer at 40–50°C until the moisture content is below 2%.
- Step 7: Pass dried granules through a finer sieve (#20) to break agglomerates and ensure uniform granule size.

5. LUBRICATION

- Step 8: Add talc and magnesium stearate to the dried granules.
- Step 9: Mix gently for 3–5 minutes in a blender (do not overmix to avoid affecting flow or dissolution)

6. COMPRESSION

- Step 10: Compress the lubricated granules into tablets using a rotary tablet press.

○ Target specifications

- Weight: As per dose (e.g., 100 mg)
- Hardness: 4–6 kg/cm²
- Thickness: ~2.5–3 mm
- Shape: Round or oval, uncoated or film-coated

7. OPTIONAL: COATING

If light protection or taste masking is needed:

- Apply a film coat using HPMC-based polymer and opacifiers (e.g., titanium dioxide).
- Use a standard pan coater or fluidized bed coater

8. PACKAGING

- Pack the tablets in light-resistant blister packs or HDPE bottles with desiccants.
- Label according to regulatory requirements

EVALUATION OF METHOTREXATE TABLET

1. APPEARANCE

- **Purpose:** To check the physical quality of tablets.
- **Procedure:** Visually inspect the tablets for color, shape, cracks, chips, and uniformity.
- **Acceptance:** Tablets should be uniform, without defects

2. WEIGHT VARIATION TEST

- **Purpose:** To ensure uniformity in tablet weight.
- **Procedure:**
  1. Weigh 20 tablets individually.
  2. Calculate the average weight.
  3. Determine the % deviation of each tablet from the average.
- **Acceptance:** For tablets <130 mg, deviation should be ±10%; for tablets 130–324 mg, ±7.5%.

3. TABLET HARDNESS

- **Purpose:** To measure the tablet's mechanical strength.
- **Procedure:** Use a Monsanto or Pfizer hardness tester to measure the force needed to break the tablet.
- **Acceptance:** 4–6 kg/cm² (typical range).

4. FRIABILITY TEST

- **Purpose:** To test tablet resistance to abrasion.
- **Procedure:**
  1. Weigh 10 tablets (W_1).
  2. Place them in a friabilator (100 revolutions at 25 rpm for 4 minutes).

3. Remove, dust, and reweigh (W_2).
4. Calculate % friability = $[(W_1 - W_2)/W_1] \times 100$

- **Acceptance:** Should be <1%.

5. DISINTEGRATION TEST

- **Purpose:** To check how quickly tablets break down in a fluid.
- **Procedure:**
    1. Place 6 tablets in the disintegration apparatus.
    2. Use 900 mL distilled water or buffer at 37 ± 0.5°C.
    3. Note the time taken for complete disintegration.
- **Acceptance:** Should disintegrate within 15 minutes (for immediate-release tablets).

6. DRUG CONTENT UNIFORMITY (ASSAY)[14]

- **Purpose:** To verify the actual amount of Methotrexate in the tablet.
- **Procedure:**
    1. Crush and weigh tablets equivalent to one dose.
    2. Dissolve in suitable solvent (e.g., phosphate buffer or NaOH).
    3. Filter and dilute appropriately.
    4. Analyse by UV-Vis spectrophotometry (λ ~302 nm) or HPLC.
- **Acceptance:** 90–110% of the label claim.

7. IN VITRO DISSOLUTION TEST

- **Purpose:** To measure the rate and extent of drug release.
- **Procedure:**
    1. Use USP Apparatus II (Paddle), 900 mL phosphate buffer (pH 6.8), 37°C, 50 rpm.
    2. At specified intervals (5, 10, 15, 30, 45, 60 min), withdraw 5 mL, filter, and analyse.
    3. Replace withdrawn volume with fresh medium.
- **Acceptance:** ≥85% of drug released in 30 minutes (for immediate release).

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