Title: Hydrogel-Based Topical Delivery for Intertrigo: Formulation with Curcumin and Tea Tree Oil

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Abstract

Intertrigo is a common inflammatory skin condition that occurs in such areas of the body where the skin folds and friction occurs. The commonly affected areas are axillae, groin, between the finger and under the breasts. It is characterised by irritation, burning, discomfort and erythema and can be intensified by heat, moisture and poor hygiene. The condition is often more complex by secondary infections, particularly fungal, bacterial or viral due to moist environment which is created by skin-to-skin contact. Obesity, diabetes and conditions that cause increased sweating are some of the risk factors. Management for this condition involves addressing the underlying causes of skin irritation reducing friction and moisture, and treating the infections with appropriate topical or systemic therapies. The key step of management is identification and correction of predisposing factors.Patients should be encouraged to lose weight, followed up properly after endocrinologic treatment and intestinal colonisation or periorificial infections should be medically managed, especially in recurrent and resistant cases. Preventive measures includes weight management, proper skin care and use of barrier products which are essential for minimising recurrence. This paper explores the clinical presentation, risk factors, pathophysiology, diagnostic approach, and evidence-based management of intertrigo, emphasising the importance of a holistic and individualised treatment plan. Additionally, future directions for research on intertrigo are discussed, highlighting gaps in understanding its molecular mechanisms and the need for improved therapeutic interventions.

Keywords: Intertrigo, Inflammatory skin condition, Skin folds, Secondary infection, Risk factors, Management, Prevention, Diagnosis, Pathophysiology, Holistic treatment.

Introduction

Intertrigo is a superficial inflammatory condition of the skin that arises predominantly in warm, moist areas where skin surfaces rub together, such as the axillae, groin, inframammary regions, and intergluteal folds. It is characterized by erythema, itching, discomfort, and in more severe cases, fissuring, maceration, and secondary infections. These infections are commonly caused by Candida albicans, dermatophytes, and bacterial agents such as Staphylococcus aureus and Corynebacterium minutissimum. Intertrigo poses a significant challenge, especially in obese individuals, diabetics, the elderly, and those with compromised immune systems due to its recurrent nature and the difficulty in maintaining dryness and hygiene in the affected areas.

Conventional treatment for intertrigo involves topical antifungals, corticosteroids, and barrier creams to alleviate inflammation, treat infections, and prevent moisture accumulation. However, frequent use of corticosteroids can lead to skin atrophy, tachyphylaxis, and increased risk of secondary infections. Similarly, the growing incidence of antimicrobial resistance necessitates the development of safer and more effective alternatives that minimize adverse effects while promoting skin healing.

Natural phytochemicals such as curcumin, derived from Curcuma longa (turmeric), and tea tree oil, extracted from Melaleuca alternifolia, have shown significant potential in dermatological applications due to their antimicrobial, anti-inflammatory, and wound-healing properties. Curcumin possesses strong antioxidant activity and modulates several molecular pathways involved in inflammation and microbial defense. Tea tree oil, rich in terpinen-4-ol, exhibits broad-spectrum antimicrobial activity and is effective against fungal and bacterial pathogens without causing significant resistance. Despite their therapeutic promise, the poor aqueous solubility and stability of these compounds limit their practical use in topical formulations.

A. TYPES, CAUSES, AND PATHOGENESIS OF INTERTRIGO

Intertrigo can be classified based on etiology:

- Acid-Related – Due to excessive sweat and moisture in folds.
- Fungal – Primarily caused by Candida species.
- Bacterial – Commonly due to Staphylococcus aureus and Streptococcus spp.
- Allergic – Resulting from allergens like soaps and fabrics (Bolognia et al., 2008).

Based on duration, it is:

- Acute – Short-term, resolves with treatment.
- Chronic – Persistent or recurrent, requiring long-term care (Janniger et al., 2005).

Pathogenesis involves friction disrupting the skin barrier, heat and moisture promoting microbial growth, and immune response triggering inflammation. Diabetic patients often

show higher pH in skin folds, predisposing them to fungal infections (Yoshipovitch et al., 1993).

B. DIAGNOSIS AND DIFFERENTIALS

Diagnosis involves:

- History & Physical Examination – Checking for redness, inflammation, and infection signs.
- Differential Diagnosis – Must rule out similar conditions like candidiasis (satellite pustules), tinea cruris, erythrasma (Wood's lamp test), herpes simplex, psoriasis, and allergic dermatitis.
- Lab Tests – KOH prep for fungal elements, bacterial cultures, and PAS staining for confirmation.

C. TREATMENT STRATEGIES

Treatment is aimed at eliminating infection, reducing inflammation, and preventing recurrence.

Topical Antifungals:

- Azoles (Clotrimazole, Ketoconazole) – Inhibit ergosterol synthesis.
- Allylamines (Terbinafine) – Inhibit squalene epoxidase.
- Ciclopirox – Interferes with fungal metabolism.
- Nystatin – Binds ergosterol to disrupt membranes.

Antibacterials:

Mupirocin and fusidic acid are used for secondary bacterial infections. Low-potency corticosteroids: Help reduce inflammation but should be used cautiously to avoid skin thinning. Lifestyle modifications such as maintaining dry skin, wearing breathable clothing, and weight management are crucial in preventing recurrence.

3. HYDROGELS IN DERMATOLOGICAL THERAPY

Hydrogels are 3D hydrophilic polymer networks capable of holding water and bioactive agents. They are biocompatible, soft, and mimic biological tissues, making them ideal for drug delivery. Nanocellulose-based hydrogels are particularly promising due to their renewability, flexibility, and non-toxicity (Thang et al., 2023; Zhu et al., 2023).

Properties of Hydrogels:

- High water absorption
- Biocompatibility

- Responsiveness to pH and temperature
- Mechanical flexibility

4. ACTIVE PHARMACEUTICAL INGREDIENTS (APIs)

a. Tea Tree Oil

Extracted from Melaleuca alternifolia, tea tree oil possesses strong antimicrobial, antifungal, and anti-inflammatory properties due to compounds like terpinen-4-ol and 1,8-cineole.

Benefits:

- Treats acne, wounds, fungal infections (e.g., athlete's foot, ringworm), and dandruff.
- Used topically, via inhalation, or in diffusers for respiratory benefits (Kairey et al., 2023).

b. Turmeric (Curcuma longa)

Turmeric contains curcuminoids like curcumin, known for anti-inflammatory, antioxidant, and wound-healing properties.

Benefits:

- Treats skin inflammation and infections
- Supports digestive and heart health
- Used topically, as a dietary supplement, or culinary ingredient (Shahrajabian et al., 2024).

5. METHODOLOGY

In this section the preparation of drug by extraction of curcumin from the crude drug of turmeric is considered meanwhile its Preformulation studies including its physical and chemical properties and its interaction with the excipients we will be using is carried out.

5.1 Extraction of curcumin from Turmeric: Crude drug of turmeric is taken and cleaned it to remove dirt present in it. After removing the dirt the crude drug is dried and then it is converted to powdered form.

Procedure –

(i) 5g of the powdered drug is weight by using weighing machine.

(ii) 50 ml of solvent (ethanol) is measured in a measuring cylinder and put in a beaker containing the weighed drug.

(iii) The mixture is stirred and then the beaker is covered with aluminium foil and kept for around 24 hours.

(iv) The mixture is then filtered with the help of filter paper and the filterate is obtained.

5.2 Pre-formulation studies on Turmeric: Pre-formulation studies were done to understand the physical and chemical properties of turmeric for hydrogel formulation.

A. Physical properties of Turmeric:

Physical properties of the drug were evaluated to understand its organoleptic properties.

a. Physical appearance:

Colour – It generally appears bright yellow to orange in colour which is due to the presence of curcumin.

Texture – When the rhizomes are fresh they are firm and fibrous, but when it is dried and powdered they become fine and slightly grainy. When powder is mixed with water it forms a paste that is smooth and firm.

Form – Found in form of whole rhizomes, powdered form or in dried pieces.

Taste – It generally tastes bitter, is slightly pungent and warm.

Odor – It smells earthy, and has a slight ginger like aroma.

b. Ph test: In this test the pH of the extract is evaluated so as to ensure whether its pH is near to the turmeric or not. The extract is taken in a test tube and a few drops of phenolphthalein is added to it. It appears pink in colour which means its pH is around 8.2 – 10.

c. Melting point: The melting point of the turmeric extract is checked my heating the extracted curcumin which is around 183 to 185 C.

B. Solubility Studies of Curcumin in Various Excipients Solubility testing was performed to evaluate the compatibility and solubilizing potential of various excipients with curcumin. This is a critical step in pre-formulation studies, as curcumin is known to possess poor aqueous solubility, which limits its bioavailability. The solubility of curcumin was assessed in different solvents commonly used in pharmaceutical formulations. The observations are as follows:

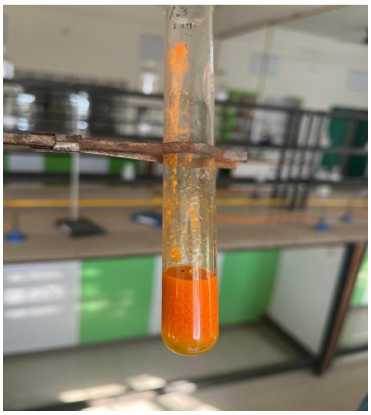
a) Solubility in Sodium Lauryl Sulfate (SLS) Curcumin was found to be soluble in sodium lauryl sulfate (SLS). SLS is an anionic surfactant that lowers the surface tension between molecules and can form micelles in aqueous media. Curcumin, being lipophilic in nature, partitions into the hydrophobic core of these micelles, thereby improving its apparent solubility. This mechanism makes SLS a useful solubilizer for poorly water-soluble drugs like curcumin.

b)Solubility in Water

Curcumin demonstrated poor solubility in water, consistent with its hydrophobic and polyphenolic structure. The molecule lacks sufficient ionizable or hydrophilic functional groups to interact favorably with water molecules, leading to minimal dissolution. This poor aqueous solubility poses a significant formulation challenge for curcumin.

c)Solubility in Propylene Glycol

Curcumin showed partial solubility in propylene glycol. Propylene glycol is a moderately polar solvent often used to improve the solubility of lipophilic compounds. While it does enhance curcumin's solubility to some extent, it does not achieve complete dissolution under ambient conditions. Mild heating can improve solubility further, but it remains suboptimal compared to more lipophilic solvents or surfactant systems.



C. Determination of Partition Coefficient of Curcumin This study was conducted to determine the partition coefficient (P) of curcumin using benzene and water as the two immiscible solvents.

1. Sample Preparation:

A known quantity of curcumin powder was weighed and added to a separating funnel containing 20 mL of benzene and 20 mL of distilled water.

2. Mixing:

The contents of the separating funnel were vigorously shaken for several minutes to allow curcumin to distribute between the two immiscible phases.

3. Phase Separation:

The funnel was allowed to stand undisturbed for a few minutes to facilitate clear separation of the aqueous and organic (benzene) layers.

4. Collection of Phases:

After complete separation, both layers were carefully collected into separate beakers.

5. Estimation of Curcumin Concentration:

The concentration of curcumin in each phase was determined using titrimetric analysis.

6. Estimation of Curcumin Concentration in Aqueous Phase

To determine the concentration of curcumin in the aqueous layer, an acid-base titration was performed using 0.1 M sodium hydroxide (NaOH) as the titrant and phenolphthalein as the indicator. To determine the concentration of curcumin in organic layer back titration was performed using 0.1 M HCL as titrant and phenolphthalein as indicator. The concentration of curcumin in the aqueous layer was found to be 1.84 mg/mL, as determined by titration with 0.1 M NaOH and the concentration of curcumin in organic layer was found to be 29.47mg/mL.

Partioncoefficiuent was found to be 16.02.

4.3 Formulation of Hydrogel

1. Preparation of Chitosan Base:

    - Accurately weighed 0.75 g of chitosan was dispersed in 30 mL of 1% v/v acetic acid.
    - The mixture was stirred continuously until a clear, homogeneous solution was obtained.

2. Solubilization of Active Ingredients:

    - 0.25 g of curcumin and 0.075 g of propylparaben were dissolved in 2–3 mL of ethanol.
    - The solution was gently heated with stirring to facilitate complete solubilization.

3. Incorporation of Humectants:

- To the chitosan solution, 2.5 mL of glycerin and 5.0 mL of propylene glycol were added.
- The mixture was stirred thoroughly to ensure uniform blending.

4. Addition of Curcumin-Paraben Solution:

- The pre-dissolved curcumin and propylparaben solution was gradually introduced into the chitosan base under continuous stirring.

5. Incorporation of Antioxidant:

- 0.5 g of ascorbic acid was directly added to the mixture.
- Stirring was continued until the ascorbic acid was fully dissolved.

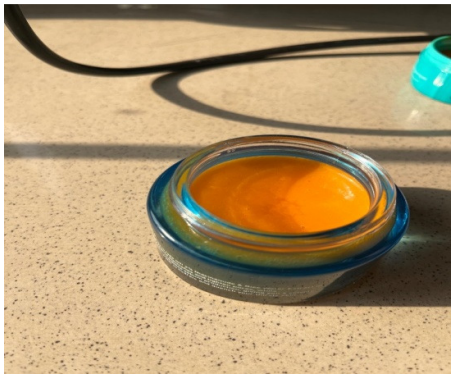
6. Addition of Fragrance and Solubilizer:

- A mixture of 0.1 mL rose oil and 0.5 mL polysorbate 80 was prepared.

- This was slowly incorporated into the formulation under stirring to ensure even distribution.

7. Initiation of Gelation:

- 0.15 g of calcium chloride was dissolved in 1–2 mL of distilled water.
- The solution was added slowly to the chitosan mixture under gentle stirring to initiate ionic crosslinking and form the hydrogel network.



5. CONCLUSION

Curcumin was successfully extracted from turmeric using ethanol, producing a bright yellow filtrate indicative of its presence. Preformulation studies confirmed its characteristic organoleptic properties and identified challenges such as poor water solubility and high lipophilicity. Curcumin showed high solubility in sodium lauryl sulfate (SLS), moderate solubility in propylene glycol, and negligible solubility in water and propylparaben. Its basic pH (8.2–10), high melting point (183–185°C), and strong preference for lipophilic environments (partition coefficient: 29.47 mg/mL in organic phase vs. 1.84 mg/mL in aqueous phase) were consistent with its known properties.

To address solubility limitations, a chitosan-based hydrogel was formulated incorporating solubilized curcumin, humectants (glycerin, propylene glycol), an antioxidant (ascorbic acid), a solubilizer (polysorbate 80), fragrance (rose oil), and preservative (propylparaben). Gelation was initiated using calcium chloride, resulting in a stable, uniform, yellow-orange hydrogel. The formulation leveraged chitosan's biocompatibility and hydration capacity, offering a promising delivery system for enhancing the topical availability of curcumin.

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