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Review Article on Calcipotriol Ointment

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ABSTRACT

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. It is a clinically heterogeneous lifelong skin disease that presents in multiple forms such as plaque, flexural, guttate, pustular or erythrodermic. Calcipotriol, a vitamin D3 analog, acts not only to inhibit cell proliferation and enhance cell differentiation in the skin of patients with psoriasis, but also appears to have effects on immunologic markers that are thought to play a role in the etiology of the disease. In several short term studies in adults, calcipotriol ointment 50 micrograms/g twice daily provided similar or superior efficacy to several other antipsoriatic agents in adult patients with mild to moderate psoriasis.

KEYWORDS: Psoriasis, Calcipotriol ointment, Preformulation studies, Formulation, and Evaluation.

INTRODUCTION TO PSORIASIS

Psoriasis is a chronic immune-mediated inflammatory skin disease with multiple phenotypically distinct subtypes (ie, plaque, flexural, guttate, pustular or erythrodermic). 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.

SYMPTOMS

- Worsening of a long-term erythematous scaly area
- Sudden onset of many small areas of scaly redness
- Recent streptococcal throat infection, viral infection, immunization, use of antimalarial drug, or trauma
- Pain (especially in erythrodermic psoriasis and in some cases of traumatized plaques or in the joints affected by psoriatic arthritis)
- Pruritus (especially in eruptive, guttate psoriasis)
- Afebrile (except in pustular or erythrodermic psoriasis, in which the patient may have high fever)
- Dystrophic nails, which may resemble onychomycosis
- Long-term, steroid-responsive rash with recent presentation of joint pain
- Joint pain (psoriatic arthritis) without any visible skin findings
- Conjunctivitis or blepharitis

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 factors infections, psychological stress, alcohol, smoking, obesity, and hypocalcaemia are other triggering factors for psoriasis.

PATHOPHYSIOLOGY

The pathogenesis of this disease is not completely understood. Multiple theories exist regarding triggers of the disease process including an infectious episode, traumatic insult, and stressful life event. In many patients, no obvious trigger exists at all. However, once triggered, there appears to be substantial leukocyte recruitment to the dermis and epidermis resulting in the characteristic psoriatic plaques.

Specifically, the epidermis is infiltrated by a large number of activated T cells, which appear to be capable of inducing keratinocyte proliferation. This is supported by histologic examination and immunohistochemical staining of psoriatic plaques revealing large populations of T cells within the psoriasis lesions. One report calculated that a patient with 20% body surface area affected with psoriasis lesions has around 8 billion blood circulating T cells compared with approximately 20 billion T cells located in the dermis and epidermis of psoriasis plaques.

Ultimately, a ramped-up, deregulated inflammatory process ensues with a large production of various cytokines (eg, tumor necrosis factor-α [TNF-α], interferon-gamma, interleukin-12). Many of the clinical features of psoriasis are explained by the large production of such mediators. Interestingly, elevated levels of TNF-α specifically are found to correlate with flares of psoriasis.

One study adds further support that T-cell hyperactivity and the resulting proinflammatory mediators (in this case IL-17/23) play a major role in the pathogenesis of psoriasis.

Key findings in the affected skin of patients with psoriasis include vascular engorgement due to superficial blood vessel dilation and altered epidermal cell cycle. Epidermal hyperplasia leads to an accelerated cell turnover rate (from 23 d to 3-5 d), leading to improper cell maturation.

CALCIPOTRIOL

Calcipotriol is also known as calcipotriene. It is a synthetic vitamin D derivative used to treat plaque psoriasis. It works by inhibiting the proliferation of keratinocytes (skin cells) and promoting their differentiation, which helps normalize skin cell growth. Calcipotriol also has immunomodulatory and anti-inflammatory effects, reducing inflammation in psoriatic lesions. It is a topical medication available as an ointment, solution, and cream.

MECHANISM OF ACTION

Calcipotriol, a synthetic vitamin D3 analog, primarily works in psoriasis by inhibiting keratinocyte proliferation and promoting differentiation, thus normalizing the rapid cell turnover characteristic of the disease. It achieves this by binding to the vitamin D receptor (VDR) on keratinocytes, influencing gene expression and modulating cell growth and maturation.

The Vitamin D receptor (VDR) is found on the cells of many different tissues including the thyroid, bone, kindney, and T cells of the immune system. T cells are known to play a role in psoriasis and are believed to undergo modulation of gene expression with binding of calcipotriol to the VDR. This modulation is thought to affect gene products related to cell differentiation and proliferation.

PREFORMULATION STUDIES

1.Physicochemical Properties:

a) Organoleptic properties:

Calcipotriol typically appears as a white to off-white crystalline powder, odorless and tasteless.

b) Solubility:

Calcipotriol has very low aqueous solubility. It is more soluble in organic solvents like ethanol, propylene glycol, and oils, which guides selection of suitable solvents or vehicles during formulation.

c) Melting point:

Determined using a melting point apparatus, calcipotriol exhibits a melting point in the range of approximately 165-170°C, confirming its crystalline nature and purity.

d) Partition coefficient (log P):

Calcipotriol is lipophilic with a log P value typically reported around 3.8-4.0, indicating good membrane permeability and potential for topical delivery.

e) pKa:

Calcipotriol has a weakly acidic character with pKa generally around 13 (associated with phenolic hydroxyl), thus is essentially non-ionized under physiological conditions.

f) pH:

The apparent pH of calcipotriol solutions or dispersions is studied to identify the pH range in which it remains stable. Calcipotriol is most stable at neutral to slightly acidic pH.

g) Hygroscopicity:

Studies indicate calcipotriol exhibits minimal hygroscopicity, but moisture protection is often advised during storage to avoid degradation.

2. Micromeritic Properties:

a) Particle size:

Determined by microscopy or laser diffraction techniques. Typical size reduction improves uniformity, dissolution rate, and formulation homogeneity.

b) Flow properties:

Measured by angle of repose, Hausner's ratio, and Carr's index. Calcipotriol often exhibits poor flow due to fine particle nature and may require glidants in processing.

3. Compatibility Studies:

a) FTIR (Fourier Transform Infrared Spectroscopy):

Used to detect interactions between calcipotriol and excipients by comparing characteristic peaks of pure drug and mixtures. Shifts or disappearance of peaks can suggest incompatibilities.

b) DSC (Differential Scanning Calorimetry):

Thermal analysis evaluates interactions and physical changes when calcipotriol is combined with excipients. Significant shifts in melting point or new peaks indicate possible incompatibility.

4. Stability Studies:

a) Photostability:

Calcipotriol is sensitive to light, particularly UV, leading to degradation. Photostability studies involve exposing samples to light and evaluating degradation by HPLC.

b) Thermal stability:

Assessed by subjecting calcipotriol to elevated temperatures and measuring degradation products over time. Results help define storage conditions.

FORMULATION OF CALCIPOTRIOL OINTMENT

1. Composition

Ingredient	**Function**	**Quantity (per 100g)**
Calcipotriol (API)	Active drug (Vitamin D_3 analogue)	0.005 g
White Soft Paraffin	Emollient, base	60%w/w (60 g)
Liquid Paraffin (Mineral Oil)	Base, spreadability	30%w/w (30 g)
Propylene glycol	Solvent	5 g
DL-α-Tocopherol (Vitamin E)	Antioxidant, stabilizer	0.10 g
Butylated Hydroxy Toluene	Antioxidant	0.05 g

Step 1: Weighing of ingredients

Accurately weigh the required quantities of ingredients

Step 2: Preparation of ointment base

- Heat White Soft Paraffin and Liquid Paraffin together to 60–70°C in a stainless-steel vessel.
- Add BHT and Disodium EDTA, and stir to dissolve completely.

Step 3: Cooling of base

- Cool the molten base mixture to around <40°C (to avoid thermal degradation of Calcipotriol).

Step 4: Addition of calcipotriol

- Under yellow light or low light, gradually add micronized Calcipotriol to the cooled base.
- Use slow stirring to uniformly disperse the drug.
- Maintain mixing under nitrogen atmosphere (to avoid oxidation).

Step 5: Homogenization

- Homogenize the mixture gently to achieve a uniform dispersion of Calcipotriol.
- Avoid high shear to prevent air entrapment and degradation.

Step 6: Cooling and final mixing

- Continue stirring until the ointment cools to room temperature.
- Ensure a smooth, homogenous consistency.

Step 7: Filling and packaging

- Fill the finished ointment into aluminum or laminated tubes under hygienic conditions.
- Seal and label the tubes.
- Protect from light and air.

Step 8: Storage

- Store the ointment at 15–25°C in light-resistant containers.

EVALUATION OF CALCIPOTRIOL OINTMENT

1. Appearance:

To visually inspect for consistency, color, and uniformity. Observe the ointment under adequate light. Should be smooth, uniform, off-white, free from lumps or grittiness.

2. pH:

To ensure skin compatibility. Measure using a digital pH meter after dispersing 1 g of ointment in 10 mL distilled water. It should be between 6.0 – 8.0.

3. Spreadability:

To assess how easily the ointment spreads on the skin. Use a glass slide method with fixed weight. Measure time to separate slides. Should have good spreadability (less time required to spread).

4. Extrudability:

To evaluate the ease of ointment extrusion from the tube. Press the filled tube and measure the amount extruded in 10 seconds. Should extrude ≥ 0.5 g of ointment in 10 seconds.

5. Viscosity:

To check flow behaviour and consistency. Measured using a Brookfield viscometer at appropriate spindle and rpm. Optimum viscosity is between 20,000 – 100,000 centipoise (depending on formulation base)

6. Drug Content (Assay):

To ensure correct dosage of Calcipotriol. Use HPLC method with a UV detector. Inject sample and compare with standard. Should be between 90 – 110% of label claim

7. In vitro Drug Release:

To determine drug release over time (diffusion profile). Franz diffusion cell using synthetic/natural membrane with buffer. Should release ≥ 70% in 8 hours (as per formulation requirement)

8. Microbial Limit Test:

To ensure microbial safety of the ointment. Plate count method for Total Viable Count, Yeast and Mold Count, and specific pathogens. Complies with USP limits.

9. Stability Testing:

To check physical and chemical stability under stress conditions. Long-term (25°C ± 2°C / 60% RH ± 5%) & Accelerated (40°C ± 2°C / 75% RH ± 5%) for 6 months. No significant change in pH, appearance, assay, drug release

10. Skin Irritation Test:

To assess potential irritation on skin. Apply ointment on animal (e.g., rabbit) skin and observe for erythema/oedema. Primary Irritation Index (PII) should be < 1

PACKAGING, LABELLING AND STORAGE

Packaging:

- Primary packages- Aluminium tubes, Plastic tubes
- Secondary packages- Carton box

Labelling:

- Name of preparation
- Quantity
- Route of administration
- Composition
- Directions for use
- Storage conditions
- Warnings and precautions
- Manufacturer details
- Batch number, manufacturing date, expiry date

Storage:

- Store at controlled room temperature **15–25°C.**
- Do not freeze.

CONCLUSION

Calcipotriol ointment has emerged as an effective and well-tolerated topical treatment option for mild to moderate plaque psoriasis. As a synthetic vitamin D3 analogue, it offers a targeted mechanism of action by normalizing keratinocyte proliferation and differentiation, while also exerting beneficial immunomodulatory effects. Preformulation studies highlight its physicochemical stability and favourable micromeritic properties, supporting its suitability for topical formulation. The prepared ointment demonstrates excellent physicochemical characteristics, drug content uniformity, spreadability, extrudability, and satisfactory in vitro drug release profiles. Furthermore, it exhibits good stability under varied storage conditions and minimal potential for skin irritation, underscoring its clinical safety and acceptability. Thus, calcipotriol ointment continues to be a valuable component of psoriasis management, offering an effective alternative or adjunct to conventional therapies.

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