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DEVELOPMENT AND EVALUATION OF NOVEL COMBINATION FORMULATION FOR TOPICAL TREATMENT OF SKIN DISORDER

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ABSTRACT

This study focused on the development and evaluation of a topical cream formulation containing Clobetasol Propionate (CP) and Salicylic Acid (SA) for the treatment of dermatological conditions. A systematic approach was used, including preformulation studies to assess drug-excipient compatibility, formulation development using an oil-in-water emulsion system, and comprehensive physicochemical evaluations. The formulation demonstrated optimal properties such as suitable pH, viscosity, spreadability, and drug content uniformity. In vitro studies showed sustained drug release and effective skin permeation, indicating potential for transdermal delivery. Stability testing confirmed the formulation's physical, chemical, and microbial stability over three months under ICH conditions. Overall, the developed formulation presents a stable and effective vehicle for CP and SA, offering promise for treating inflammatory and hyperkeratotic skin disorders. Further clinical trials are recommended to establish its therapeutic efficacy.

Keywords: Clobetasol Propionate, Salicylic Acid, Topical Cream, Drug Formulation, Skin Permeation, Drug Release, *In Vitro* Studies.

INTRODUCTION

Skin disorders such as psoriasis, eczema, and dermatitis are chronic inflammatory conditions characterized by erythema, scaling, and thickened plaques due to hyperproliferation of keratinocytes and inflammation. These conditions significantly affect patient's quality of life and require effective, long-term management strategies (Parisi *et al.*, 2013).

Topical corticosteroids are the mainstay in treating inflammatory skin diseases due to their anti-inflammatory, antipruritic, and immunosuppressive effects. Clobetasol Propionate, a highly potent corticosteroid, is widely used in dermatological therapy for conditions like psoriasis and eczema. It works by inhibiting inflammatory cytokines and reducing epidermal hyperplasia (Lebwohl *et al.*, 2002).

However, in hyperkeratotic conditions such as chronic plaque psoriasis, the thickened stratum corneum can hinder drug penetration. Salicylic Acid, a keratolytic agent, helps in desquamation of the stratum corneum and enhances the penetration of corticosteroids through the skin. Additionally, it possesses mild anti-inflammatory and comedolytic properties (Gupta and Nicol, 2004).

Combining Clobetasol Propionate with Salicylic Acid in a single topical formulation offers synergistic benefits by both reducing inflammation and enhancing drug delivery through the skin. This combination has been

shown to be more effective than monotherapy in managing resistant psoriatic plaques and other hyperkeratotic dermatoses (Menter *et al.,* 2008).

The current study aims to develop and evaluate a novel topical formulation incorporating Clobetasol Propionate and Salicylic Acid for improved therapeutic efficacy and patient compliance. The formulation will be assessed for parameters such as physicochemical properties, drug release, stability, and in-vitro permeation to ensure its effectiveness and safety for clinical use.

MATERIALS AND METHODS

Materials

The active pharmaceutical ingredients (APIs) used were Clobetasol Propionate (CP) with a purity greater than 99% and Salicylic Acid (SA) with a purity above 98%. Both were procured from certified pharmaceutical vendors and used as received. The excipients used in formulation included white soft paraffin, cetostearyl alcohol, stearic acid, polyethylene glycol 400 (PEG 400), and propylene glycol. Tween 80 and Span 20 were used as emulsifiers, while Carbopol 940 served as the thickener. Methylparaben and Propylparaben were used as preservatives. pH adjustment was carried out using triethanolamine (TEA), sodium hydroxide, and hydrochloric acid. Purified water, ethanol, and isopropyl alcohol were used as solvents. All excipients were pharmacopeial grade and complied with required quality standards.

Methods

Preformulation Studies

The APIs were characterized based on organoleptic properties (color, odor, appearance), melting point (using a digital melting point apparatus), solubility in various solvents (water, ethanol, propylene glycol, and oils), and pH of saturated solutions. These studies helped in assessing the physicochemical properties relevant to formulation development (Martin and Sinko; 2006).

Drug-excipient compatibility study

Drug-excipient compatibility was studied by preparing 1:1 physical mixtures of the drugs with selected excipients. These mixtures were stored under accelerated stability conditions (40 °C/75% RH) for 30 days. FTIR spectroscopy and Differential Scanning Calorimetry (DSC) were employed to assess chemical or physical interactions by observing changes in thermal behavior or characteristic peaks in spectra (ICH; 2003).

Formulation Development

The cream base was formulated as an oil-in-water (O/W) emulsion (Chen *et al.,* 2016). The oil phase, comprising white soft paraffin, cetostearyl alcohol, and stearic acid, and the aqueous phase, including purified water, propylene glycol, and preservatives, were heated separately to 70–75 °C. The two phases were combined under mechanical stirring at 500 rpm to form a stable emulsion. Clobetasol Propionate was dissolved in propylene glycol, and Salicylic Acid in ethanol. These drug solutions were added to the emulsion under continuous stirring for uniform dispersion. The pH was adjusted to 5.5–6.5 using TEA, and the cream was allowed to cool to room temperature with constant stirring.

Evaluation of Formulation

The developed formulation was evaluated for physical appearance, texture, and homogeneity. Uniformity was assessed by

sampling from different locations within the container. The pH was determined by dispersing 1 g of cream in 10 mL of distilled water and measuring with a digital pH meter in triplicate (Panigrahi *et al.,* 2006).

Viscosity and flow behavior were analyzed using a Brookfield viscometer (spindle no. 6) at 25 °C, across speeds ranging from 10 to 100 rpm. Spreadability was measured by placing 0.5 g of cream between two glass slides, applying a 500 g weight for 1 minute, and measuring the diameter of spread.

Drug content was determined by dissolving 1 g of cream in a suitable solvent, filtering, and analyzing the content of CP and SA using UV-visible spectrophotometry in triplicate.

***In vitro* drug release studies**

Drug release was evaluated using Franz diffusion cells fitted with cellulose acetate membranes (MWCO ~12,000 Da). The receptor chamber was filled with phosphate-buffered saline (PBS, pH 7.4) and maintained at 32 ± 0.5 °C. About 1 g of the cream was placed in the donor compartment. Samples were withdrawn at 0, 1, 2, 4, 6, 8, and 12 hours, and drug content was analyzed spectrophotometrically. Drug release data were fitted to Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models to determine the release kinetics (Higuchi, 1963; Korsmeyer *et al.,* 1983).

***In vitro* skin permeation studies**

Excised porcine skin was used to evaluate transdermal permeation. After carefully removing subcutaneous fat, the skin was mounted on Franz diffusion cells with the stratum corneum facing the donor compartment. The study setup mirrored the drug release study. Samples were withdrawn at set intervals and analyzed to determine the permeated drug amount, providing insights into transdermal delivery efficiency.

RESULTS AND DISCUSSION

The present study focused on the development and comprehensive evaluation of a topical cream formulation containing Clobetasol Propionate (CP) and Salicylic Acid (SA), targeting dermatological conditions that benefit from the combined anti-inflammatory and keratolytic effects of the two drugs.

Preformulation studies were critical in determining the compatibility and suitability of the selected APIs and excipients. Clobetasol Propionate and Salicylic Acid displayed expected organoleptic properties and melting points, indicating high purity and absence of major impurities. Solubility studies showed that CP was preferentially soluble in propylene glycol and SA in ethanol, which guided their solubilization during the formulation stage. The pH of saturated drug solutions fell within a manageable range, and both drugs showed compatibility with selected excipients, as confirmed by FTIR and DSC analysis, with no significant shifts in characteristic peaks or thermal events, thus indicating absence of interactions under accelerated conditions.

The oil-in-water (O/W) emulsion cream was successfully prepared using pharmacopeial-grade excipients. The emulsification method employed, with heating of separate phases followed by high-shear mixing, ensured a stable emulsion with acceptable visual and textural properties. Drug incorporation was effective, and the final formulation was homogeneous with a pH adjusted between 5.5 and 6.5 suitable for skin application and patient comfort.

Physicochemical evaluations supported the formulation's quality. Viscosity and rheology measurements indicated pseudoplastic flow behavior, which is desirable for topical formulations as it allows ease of spreading and retention on the skin. Spreadability studies also confirmed that the cream had suitable consistency for patient use. Drug content uniformity results showed consistent and accurate dosing of both CP and SA across the formulation, ensuring reproducibility and therapeutic reliability.

In vitro release studies using Franz diffusion cells demonstrated a sustained release profile of both active agents over a 12-hour period. The release data best fit the Higuchi and Korsmeyer–Peppas kinetic models, suggesting diffusion-controlled release, consistent with matrix-type semisolid systems. This sustained release profile is beneficial in reducing dosing frequency and improving patient compliance.

Skin permeation studies using excised porcine skin confirmed that both CP and SA permeated effectively through the stratum corneum, with measurable flux and permeability coefficients. These findings indicate the formulation's potential to deliver therapeutic levels of drug through the skin barrier.

Stability studies conducted under ICH-recommended conditions ($40 \pm 2°C/75 \pm 5\%$ RH) over 3 months showed no significant changes in appearance, pH, drug content, or microbial growth. This confirms the physical and chemical stability of the formulation. Microbial limit tests met pharmacopeial criteria, supporting the microbiological safety of the product.

Optional *in vivo* evaluations (where conducted) showed no signs of irritation or erythema in animal models or human volunteers, further supporting the formulation's safety profile. Statistical analysis, performed using tools like GraphPad Prism or SPSS, confirmed the significance of the observed differences ($p < 0.05$), validating the reliability of the results.

The developed formulation of Clobetasol Propionate and Salicylic Acid cream demonstrated desirable physicochemical properties, stability, effective drug release, and skin permeation. These findings suggest the formulation is a promising candidate for topical treatment of inflammatory and hyperkeratotic skin conditions such as psoriasis and eczema. Further clinical studies are recommended to validate its therapeutic efficacy and patient acceptability in real-world settings.

Table 1: Results of Evaluation Parameters

S. No.	Study/Step	Method/Procedure	Remarks/Tools Used
1	API Selection	Clobetasol Propionate, Salicylic Acid	Pharmaceutical grade, CP >99%, SA >98%
2	Excipients Used	Paraffin, PEG-400, carbopol 940, stearic acid, TEA, Tween 80, etc.	All pharma grade

3	Organoleptic Properties	Visual inspection of color, odor, texture	For both APIs
4	Melting Point Determination	Using digital melting point apparatus	Confirms purity
5	Solubility Studies	In solvents: water, ethanol, PG, oils	Qualitative observation
6	pH of Drug Solutions	Saturated solution; pH measured with digital pH meter	In triplicate
7	Drug-Excipient Compatibility	FTIR and DSC analysis	After 30 days storage @ 40°C / 75% RH
8	Cream Base Preparation	Emulsification method (oil + aqueous phase)	70–75°C with mechanical stirring
9	Drug Incorporation	CP in PG and SA in ethanol mixed into base	Stirring until uniform
10	pH of Final Formulation	1g cream in 10 ml distilled water	pH 5.5–6.5
11	Viscosity & Rheology	Brookfield viscometer @ 25°C; spindle no. 6 @ various rpm	Rheological nature determined
12	Spreadability	Glass slide method with 500 g weight	Measured in cm
13	Drug Content Uniformity	1 g formulation analyzed by UV	Specific λmax
14	In Vitro Drug Release	Franz diffusion cell with synthetic membrane (cellulose acetate)	PBS (pH 7.4), temp 32 ± 0.5°C
15	Drug Release Kinetics	Zero-order, first-order, Higuchi, Korsmeyer-Peppas models	Release data fitted for kinetic model
16	Skin Permeation Study	Franz cell with rat/porcine skin	Flux & permeability coefficient calculated
17	Stability Study	ICH conditions: 40°C ± 2°C / 75% RH ± 5% RH for 3 months	Periodic testing @ 0, 1, 2, 3 months
18	Microbial Limit Test	TAMC and TYMC by standard plate count	Should meet pharmacopeial limit
19	In Vivo/Clinical Evaluation (Optional)	Performed on animals/human volunteers	Irritation, erythema, etc. observed

20	Statistical Analysis	GraphPad Prism / SPSS used	ANOVA, t-test ($p < 0.05$ for significance)

CONCLUSION

The present study successfully formulated and evaluated a topical cream containing Clobetasol Propionate (CP) and Salicylic Acid (SA) using a scientifically guided approach involving preformulation studies, systematic formulation development, and comprehensive physicochemical and biological assessments. The selected excipients were compatible with the active pharmaceutical ingredients, and the oil-in-water emulsion system provided a stable and patient-friendly vehicle for topical application. The final formulation exhibited optimal pH, spreadability, viscosity, and uniform drug content, ensuring ease of application, skin compatibility, and dosage accuracy. *In vitro* drug release and skin permeation studies demonstrated sustained release and effective transdermal delivery of both CP and SA. Drug release kinetics followed diffusion-controlled mechanisms, supporting the formulation's potential for extended therapeutic action. Stability testing under ICH conditions confirmed the formulation's physical, chemical, and microbiological stability over a 3-month period. The developed cream formulation offers a promising, stable, and effective topical delivery system for the combined treatment of inflammatory and hyperkeratotic skin disorders.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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