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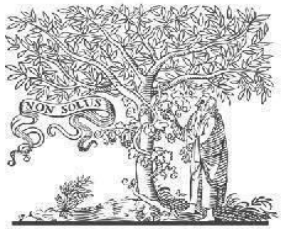

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Paper Authors
Niranjan Babu Mudduluru

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DEVELOPMENT AND CHARACTERIZATION OF DAPSONE TOPICAL GEL FOR TREATING LEPROSY

Niranjan Babu Mudduluru
Department of Pharmacognosy, Seven Hills College of Pharmacy, Tirupati, A.P., India

Corresponding Author: Dr. M. Niranjan Babu
Professor, Department of Pharmacognosy, Seven Hills College of Pharmacy, Tirupati, A.P., India – 517561
7702484513, principal.cq@jntua.ac.in

Abstract:
Leprosy, also known as Hansen's disease, presents a significant global health challenge, varying in severity from tuberculoid to lepromatous forms (paucibacillary to multibacillary illness) depending on the host's immune response. Orally administered dapsone has been associated with hematologic side effects like methemoglobinemia, hemolysis, and agranulocytosis, particularly in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Topical therapies mitigate these risks by reducing systemic exposure. The primary objective of this study is to achieve effective drug concentrations at the targeted site of action over sufficient durations to achieve therapeutic efficacy.

Key Words: Dapsone, Topical Gel, Pharmaceutical, Leprosy, Cutaneous Disorder.

Introduction:

Topical delivery refers to the application of pharmaceutical dosage forms onto the skin to directly treat cutaneous disorders, aiming to localize the pharmacological effects of drugs on the skin surface. Topical drug delivery systems encompass semisolids, liquid preparations, sprays, and solid powders. Among semisolid preparations, gels, creams, and ointments are commonly used.

Gels are characterized as semi-rigid systems where the movement of the dispersing medium is constrained by a three-dimensional network of particles or solvated macromolecules of the dispersed phase [1].

Leprosy, also known as Hansen's disease, is a global health concern characterized by a spectrum from tuberculoid to lepromatous forms (paucibacillary to multibacillary disease) based on the host's immune response. It is caused by Mycobacterium leprae, affecting the skin, eyes, and nerves, leading to skin lesions, eye pain, vision loss, weakness, and numbness. Diagnosis involves skin biopsy, smear tests, and physical examination. Treatment options vary with clinical manifestations and may include type 1 (reversal) and type 2 (erythema nodosum leprosum) immunologic reactions occurring before, during, or after treatment initiation.

Oral administration of dapsone (DAP) is associated with adverse effects such as hemolytic anemia, peripheral neuropathy, nausea, and headache, limiting its suitability for oral

treatment of skin diseases. Many of these effects are linked to DAP metabolites. N-acetyltransferase acetylates DAP in the liver to produce mono-acetyl DAP, while enzymatic hydroxylation yields DAP hydroxylamine, primarily responsible for adverse effects. Given DAP's therapeutic importance, reducing its adverse effects through nanotechnology is desirable.

Most infections caused by Gram-positive organisms can be effectively treated with a small range of antibiotics.

Materials and Methods

Materials: Dapsone was obtained as a gift sample from Glenmark Pharmaceuticals Ltd., Mumbai, India. Carbopol 971P and methanol were procured from Grey Scientific, Ambala, while other chemicals (supplied by Loba Chemicals Pvt. Ltd., Mumbai) were purchased locally. All reagents used were of analytical grade for the development of the topical gels.

Preparation of Antimicrobial Gel

Carbopol 924 was dispersed in 5 ml of distilled water under continuous stirring and left overnight for swelling. DAPSONE and PEG 400 were then added to the mixture, and the volume was adjusted to 10 ml by adding the remaining distilled water. The entire mixture was thoroughly mixed with Carbopol 924 to achieve a smooth antimicrobial gel. Finally, different formulations were prepared to adjust the pH to approximately 4.5-5.5, ensuring the gel had the desired consistency. The prepared antimicrobial gel underwent various evaluation parameters. Gels can be prepared using the ratios of ingredients outlined [2].

S.No.	Ingredients	F1	F2	F3
1.	Dapsone	100mg	100mg	100mg
2.	Carbopol 924	0.15 gm	0.15 gm	0.15 gm
3.	Ethanol	0.4 ml	0.4 ml	0.4 ml
4.	PEG 400	0.5 gm	0.5 gm	0.5 gm
5.	Distilled water	10 ml	10 ml	10 ml

Table 1. Depicting formulation of anti-microbial gel

Evaluation of Antimicrobial Gel

Measurement of pH: The pH values of various formulations were measured using a calibrated digital pH meter at room temperature in triplicate [3].

Measurement of Viscosity: Viscosity measurements of the prepared gel were conducted using a Brookfield Viscometer. The gels were rotated at speeds of 0.3, 0.6, and 1.5 rotations per minute, and corresponding dial readings were recorded. Viscosity was calculated by multiplying the dial reading with the appropriate factor from the Brookfield Viscometer catalogues [4].

Homogeneity: After setting in the container, all developed gels underwent visual inspection for homogeneity. They were assessed for their appearance and the absence of any aggregates [5].

Grittiness: Microscopic evaluation of all formulations was performed to detect the presence of any significant particulate matter under a light microscope. The gel preparations were confirmed to meet the requirements for freedom from particulate matter and grittiness [6].

Antimicrobial Study

Test Organisms and Inoculums: Gram-positive: Staphylococcus aureus Gram-negative: E. coli

Media Preparation: Dehydrated nutrient agar media was prepared by suspending 28g in 1000ml distilled water. The mixture was heated on a water bath until fully dissolved, then sterilized by autoclaving at 121°C and 15 lbs per square inch pressure for 20 minutes.

Method: Cup and Plate Method Sterile nutrient agar medium (40°C to 50°C) was poured into Petri plates to a depth of 3 to 4 mm. After solidification, each plate was inoculated with 0.1ml of test organism solution. Wells were bored at the center and filled with the gel. Plates were incubated at 37°C for 24 hours, and the zones of inhibition were measured to assess antimicrobial activity.

Stability Study: Formulations underwent stability testing according to modified ICH guidelines. Samples were stored at 40±2°C/75±5% RH for 3 months. After storage, samples were evaluated for visual appearance, pH, and drug content.

TEM Study: Samples were prepared by placing a drop of gel on a carbon-coated copper grid. After absorption and removal of excess liquid, the sample was contrasted with uranyl acetate and air-dried. Transmission electron microscopy (TEM) at 90kV was used for observation.

Permeability Studies (Diffusion Cell): In vitro release studies were conducted using phosphate buffer pH 5.5 as the receptor medium. Pretreated cellophane membrane served as the diffusion barrier in the diffusion cell setup. The gel sample was applied, and the temperature was maintained at 37º±2ºC with magnetic stirring. Samples withdrawn at intervals were analyzed spectrophotometrically at 293nm against blanks.

Result and Discussion

The methods outlined in the methodology were employed for the development and evaluation of a gel containing dapsone as the active ingredient. These formulations aimed to achieve immediate drug release. The results and discussions are presented under the following headings. An anti-acne gel containing dapsone was evaluated for various parameters. In this study, eight formulations were prepared, varying in polymer concentration and using different polymers.

As detailed in the methods section, FT-IR studies were conducted on pure dapsone and in combination with the polymer. No interactions were observed between the drug and the excipients used in the gel development. The IR spectra of dapsone, carbopol 971P, and their physical mixture combinations are depicted in Figure 1 & 2 respectively, with observed peaks detailed in Table 2.

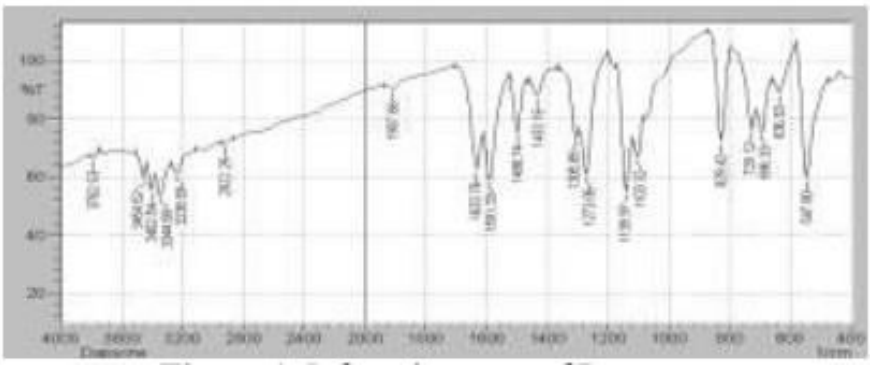

Figure1: Infrared spectral Anlaysis of Dapsone

Interpretation of chemical group	Observed peaks	Standard ranges
C-C Aromatic	1633.76	1600-1680
N-H stretch	3344.68	3100-3500
N-H bending	1633.76	1640-1550
S=Ostretch	1433.16	1140-1445

Table 2. Interpretation of Pure drug by FT-IR

DSC Thermograph of Dapsone

The melting point of dapsone was determined using Differential Scanning Calorimetry (DSC) at a scanning rate of 10°C/min. It exhibited a sharp endothermic peak corresponding to melting at a temperature of 179.86°C, as illustrated in Figure 8.

Parameters	Observed results
Melting point determination	182^0 C
DSC method	179.86^0 C
Reference range	178-83 ^{0} C

Table 3. Interpretation of DSC Thermogram of Dapsone

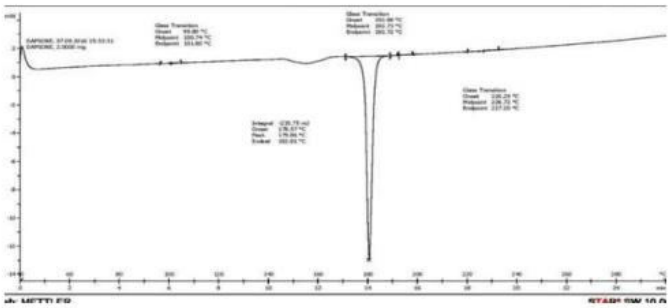

Figure 2. DSC Study of Pure Drug

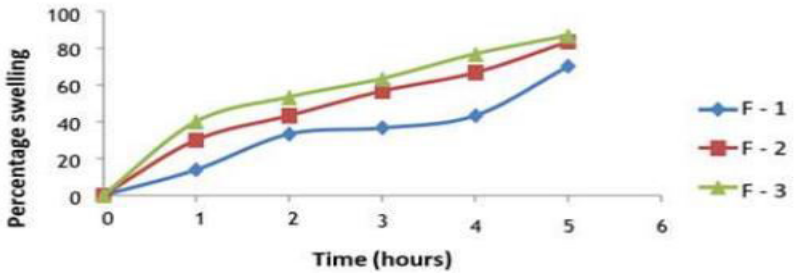

Figure 7.Percentage swelling index v/s time profile of formulations F - 1, F - 2 and F – 3

Conclusion

The treatment of leprosy poses significant challenges due to its chronic nature and the impact it has on patients, particularly adolescents who may face psychological distress. Various systemic and topical drugs are available to target different phases of leprosy, with inflammation playing a crucial role in its pathogenesis. Systemic antibiotics and anti-inflammatory drugs are integral to leprosy management.

In conclusion, the formulated gel as a topical drug delivery system shows promise in enhancing the efficacy of dapsone for treating leprosy. FTIR and DSC studies indicated no interaction between the drug and excipients used. Based on in-vitro drug diffusion studies, optimized batch F2 demonstrated 98.9% drug release within 90 minutes. This gel exhibited

clarity, transparency, neutral pH, easy viscosity adjustment, excellent spreadability, and high effectiveness in inhibiting microbial growth. Furthermore, the gel remained stable at room temperature, and quality control tests confirmed compliance with acceptable limits. Therefore, such topical drug delivery systems hold potential for future applications in leprosy treatment.

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