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## Development and Evaluation of Solid Lipid Nanoparticle-Loaded Polymeric Hydrogels Containing Dapsone.

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### ABSTRACT

Dapsone is a synthetic sulfone with antimicrobial and anti-inflammatory activity, but conventional topical formulations may provide limited skin penetration and short local retention. This study aimed to develop, optimize, and characterize a dapsone-loaded solid lipid nanoparticle (DDP-SLN) polymeric hydrogel for controlled dermal delivery. DDP-SLNs were prepared by hot homogenization followed by probe ultrasonication using glyceryl monostearate (GMS), soya lecithin, and Tween 80. A three-factor, three-level Box–Behnken design using Design-Expert® Version 13 was employed to optimize the formulation based on particle size, entrapment efficiency, and 12-h cumulative drug release. The optimized DDP-SLN dispersion was incorporated into Carbopol 934 hydrogel and evaluated for physicochemical, rheological, drug-release, and stability characteristics. The optimized DDP-SLN showed a particle size of 140.38 nm, PDI of 0.287, zeta potential of  $-35.0$  mV, and entrapment efficiency of 87.93%. The hydrogel exhibited homogeneous texture, pH of  $6.23 \pm 0.08$ , viscosity of  $8486.67 \pm 70.95$  cP, and spreadability of  $18.42$  g·cm/s. Cumulative drug release reached 87.90% over 12 h and followed the Higuchi model ( $R^2 = 0.9910$ ), while the Korsmeyer–Peppas exponent ( $n = 0.612$ ) indicated anomalous transport. The formulation remained stable under the evaluated storage conditions, demonstrating its potential as a topical delivery system for dapsone. The system was designed to enhance drug localization while providing sustained release and hydrogel performance. These findings demonstrate the suitability of combining SLN technology with a hydrogel to improve topical dapsone delivery and maintain formulation quality.

**Keywords:** Dapsone; Solid Lipid Nanoparticles; Polymeric Hydrogel; Glyceryl Monostearate; Box–Behnken Design; Carbopol 934.

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## INTRODUCTION

The human skin represents the primary physiological barrier protecting internal organs from environmental insults, xenobiotics, and pathogen invasion. Comprising three anatomically distinct layers—the epidermis, dermis, and hypodermis—the skin receives approximately one-third of total circulating blood volume and covers a total surface area of roughly 2.0 m<sup>2</sup> in an average adult <sup>[1, 2]</sup>.

The outermost layer of the epidermis, the stratum corneum, serves as the principal rate-limiting structure against the percutaneous diffusion of therapeutic agents <sup>[3]</sup>. Topologically arranged in a "bricks and mortar" architecture, the stratum corneum consists of flattened, dead, keratinized cells (corneocytes) surrounded by an extracellular, continuous lipid domain containing ceramides, free fatty acids, and cholesterol derivatives organized in densely packed lamellar bilayers <sup>[4, 5]</sup>.

Percutaneous drug delivery provides several therapeutic advantages over conventional oral or systemic routes, including avoidance of hepatic first-pass metabolism, elimination of gastrointestinal enzymatic degradation, localized tissue targeting, reduced peak-to-trough systemic concentration fluctuations, and improved patient compliance <sup>[6]</sup>. However, the dense hydrophobic packing of stratum corneum lipids restricts the transdermal transport of molecules, permitting passive penetration primarily to small, moderately lipophilic drug molecules with molecular weights below 500 Da <sup>[7, 8]</sup>.

Conventional topical formulations such as ointments, pastes, and creams frequently fail to achieve prolonged therapeutic drug levels in deeper epidermal tissues due to poor substantivity, easy removal by clothing, short retention times, and variable skin permeability <sup>[9]</sup>. To overcome these mechanical and physiological barriers, advanced nanostructured delivery platforms have been developed. Solid lipid nanoparticles (SLNs) are colloidal carrier systems ranging in size from 50 nm to 1000 nm, composed of sub-micron solid lipids dispersed within an aqueous surfactant phase <sup>[10]</sup>. SLNs offer enhanced chemical stability for labile drugs, high entrapment capacity for lipophilic molecules, lower cellular toxicity compared to polymeric nanoparticles, ease of scale-up, and an intrinsic occlusive film-forming effect on the skin surface that decreases transepidermal water loss (TEWL) and opens intercellular lipids <sup>[11, 12]</sup>.

Despite these benefits, low-viscosity aqueous dispersions of SLNs present handling challenges, such as runoff and reduced dwell time when applied topically <sup>[13]</sup>. Incorporating SLN dispersions into a polymeric hydrogel matrix bridges this gap. Polymeric hydrogels are three-dimensional, cross-linked, hydrophilic polymer networks capable of absorbing large volumes of water while retaining physical integrity <sup>[14]</sup>. Polymers such as Carbopol 934 hydrate and swell upon neutralization, forming a structured gel framework. This matrix immobilizes the lipid nanoparticles, provides

suitable rheological properties, and allows controlled release of the entrapped drug into cutaneous target areas <sup>[15]</sup>.

Dapsone (4,4'-diaminodiphenyl sulfone) is a synthetic sulfone with dual antibacterial and anti-inflammatory properties <sup>[16]</sup>. Historically utilized as a primary agent in multi-drug regimens for leprosy, Dapsone also demonstrates efficacy in managing chronic inflammatory dermatoses, including acne vulgaris, dermatitis herpetiformis, and erosive lichen planus <sup>[17, 18]</sup>. Its anti-inflammatory action stems from the inhibition of neutrophil myeloperoxidase activity, suppression of lysosomal enzyme release, scavenging of reactive oxygen species (ROS), and reduction of chemoattractant-induced neutrophil migration <sup>[19]</sup>.

When administered orally, Dapsone exhibits significant systemic toxicity, including dose-dependent hemolytic anemia, methemoglobinemia, agranulocytosis, and peripheral neuropathy, caused by hydroxylamine metabolites generated through hepatic cytochrome P450 metabolism <sup>[20]</sup>. Topical delivery minimizes systemic exposure and limits these hematological adverse events <sup>[21]</sup>. However, Dapsone's low aqueous solubility (0.2 mg/mL at 25°C) and moderate lipophilicity (log P = 0.97) can hinder cutaneous retention and cause localized crystallization when formulated in simple gels or solutions <sup>[22]</sup>.

This study evaluates the development and optimization of a Dapsone-loaded solid lipid nanoparticle polymeric hydrogel (DDP-SLN hydrogel). A 3-factor, 3-level Box-Behnken design (BBD) was utilized to evaluate the effects of solid lipid (Glyceryl monostearate), surfactant (Soya lecithin), and co-surfactant (Tween 80) concentrations on particle dimensions, encapsulation yield, and release kinetics. The optimized SLN dispersion was integrated into a cross-linked Carbopol 934 gel network to form a stable topical formulation.

## MATERIALS AND METHOD

### Materials

Dapsone (purity > 99.0%) was purchased from Yarrow Chemicals (Mumbai, India). Glyceryl monostearate (GMS) and Soya lecithin were obtained from HiMedia Laboratories Pvt. Ltd. (Mumbai, India). Tween 80, Sodium hydroxide, and Potassium dihydrogen orthophosphate were sourced from Thermo Fisher Scientific India Pvt. Ltd. (Mumbai, India). Carbopol 934 was obtained from Fine Chemicals Ltd. Double-distilled water was produced in-house using an all-glass distillation unit. All chemicals, solvents, and reagents utilized were of analytical grade.

## Preformulation Studies

### Melting Point Determination

The melting point of Dapsone was evaluated using a Thiele tube melting point apparatus filled with liquid paraffin. A capillary tube sealed at one end was packed with finely ground Dapsone powder and secured to a calibrated thermometer. Heating was applied at a rate of 1<sup>0</sup>C/min. The temperatures at which initial melting began and complete liquefaction occurred were recorded in triplicate.

### Analytical Calibration Curve of Dapsone

A primary stock solution (1.0 mg/mL) of Dapsone was prepared by dissolving 10.0 mg of the drug in 10.0 mL of methanol, followed by dilution to 100.0 mL using phosphate buffer solution (pH 6.8). Secondary dilutions were made by transferring 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, and 4.0-mL aliquots into 10.0 mL volumetric flasks and making up to volume with phosphate buffer to generate standard solutions ranging from 2.0 to 12.0 µg/mL. Solutions were scanned across the ultraviolet spectrum (200 nm to 400 nm) using a Shimadzu UV-1800 double-beam spectrophotometer to identify the maximum absorption wavelength ( $\lambda_{\text{max}}$ ). Standard absorbance values were recorded at  $\lambda_{\text{max}}$  = 295 nm against a blank solution, and a linear regression analysis was performed.

### Fourier-Transform Infrared (FTIR) Spectroscopy Studies

Compatibility between Dapsone, Glyceryl monostearate, Soya lecithin, Tween 80, Carbopol 934, and their physical mixtures was evaluated via Attenuated Total Reflectance Fourier-Transform Infrared (ATR-FTIR) spectroscopy (Bruker Alpha FTIR Spectrophotometer). Samples were placed directly onto the ATR crystal, and spectra were collected over the wavenumber range of 4000 cm<sup>-1</sup> to 400 cm<sup>-1</sup> at a resolution of 4 cm<sup>-1</sup> with 32 co-added scans. Spectra were evaluated for shift, loss, or broadening of functional group absorption peaks.

### Experimental Design (Quality by Design Approach)

A 3-factor, 3-level Box-Behnken Design (BBD) was implemented using Design-Expert® software (Version 13.0.1.0, Stat-Ease Inc., Minneapolis, MN, USA) to evaluate the impact of formulation variables on key response parameters. The independent factors selected were Glyceryl monostearate amount (A), Soya lecithin amount (B), and Tween 80 amount (C). The dependent variables evaluated were Particle Size (Y<sub>1</sub>, nm), Entrapment Efficiency (Y<sub>2</sub>, %), and Percentage Cumulative Drug Release at 12 hours (Y<sub>3</sub>, %). The independent variables and their assigned coded values (-1, 0, +1) are presented in Table 1.

**Table 1: Independent variables, coded/actual levels, and dependent responses in Box-Behnken Design**

| Dependent Variables | Units | Optimization |
|---------------------|-------|--------------|
|---------------------|-------|--------------|

| (Responses)                                       | Target   |
|---------------------------------------------------|----------|
| Y <sub>1</sub> : Particle Size nm                 | Minimize |
| Y <sub>2</sub> : Entrapment Efficiency %          | Maximize |
| Y <sub>3</sub> : % Cumulative Drug Release (12 h) | Maximize |

| Independent Variables           | Units | Low Level (-1) | Medium Level (0) | High Level (+1) |
|---------------------------------|-------|----------------|------------------|-----------------|
| Factor A: Glyceryl monostearate | mg    | 200            | 300              | 400             |
| Factor B: Soya lecithin         | mg    | 100            | 150              | 200             |
| Factor C: Tween 80              | mg    | 100            | 150              | 200             |

The design matrix comprised 17 experimental runs, including 12 factor-edge midpoints and 5 center-point replicates to estimate pure experimental error. The response values were fitted to second-order quadratic polynomial models as defined by the following equation:

$$Y = \beta_0 + \beta_1A + \beta_2B + \beta_3C + \beta_{12}AB + \beta_{13}AC + \beta_{23}BC + \beta_{11}A^2 + \beta_{22}B^2 + \beta_{33}C^2$$

Where Y is the predicted response;  $\beta_0$  is the intercept;  $\beta_1$ ,  $\beta_2$ ,  $\beta_3$  are linear coefficients;  $\beta_{12}$ ,  $\beta_{13}$ ,  $\beta_{23}$  are interaction coefficients; and  $\beta_{11}$ ,  $\beta_{22}$ ,  $\beta_{33}$  are quadratic coefficients.

The 17 formulation compositions derived from the BBD design are outlined in Table 2.

**Table 2: Composition of Dapsone-loaded solid lipid nanoparticle formulations (F1–F17) generated by BBD**

| Formulation Code | Dapsone (mg) | GMS (A, mg) | Soya Lecithin (B, mg) | Tween 80 (C, mg) | Water (mL) |
|------------------|--------------|-------------|-----------------------|------------------|------------|
| F1               | 10           | 300         | 150                   | 150              | 10         |
| F2               | 10           | 400         | 200                   | 150              | 10         |
| F3               | 10           | 200         | 200                   | 150              | 10         |
| F4               | 10           | 300         | 200                   | 200              | 10         |
| F5               | 10           | 400         | 150                   | 150              | 10         |
| F6               | 10           | 300         | 150                   | 100              | 10         |
| F7               | 10           | 400         | 150                   | 150              | 10         |
| F8               | 10           | 400         | 100                   | 150              | 10         |
| F9               | 10           | 300         | 150                   | 200              | 10         |
| F10              | 10           | 300         | 100                   | 200              | 10         |
| F11              | 10           | 300         | 200                   | 100              | 10         |
| F12              | 10           | 200         | 150                   | 150              | 10         |
| F13              | 10           | 300         | 150                   | 150              | 10         |
| F14              | 10           | 300         | 150                   | 150              | 10         |
| F15              | 10           | 200         | 150                   | 200              | 10         |
| F16              | 10           | 300         | 100                   | 100              | 10         |
| F17              | 10           | 200         | 100                   | 150              | 10         |

### Preparation of Dapsone-Loaded Solid Lipid Nanoparticles (DDP-SLNs)

Dapsone-loaded SLNs were prepared using hot high-speed homogenization followed by probe ultrasonication.

1. **Lipid Phase Preparation:** Glyceryl monostearate was placed in a glass beaker and heated on a thermostatically controlled magnetic hotplate to 75°C (approximately 10°C above its melting point). Dapsone (10.0 mg) was added to the molten lipid and stirred continuously until dissolved.
2. **Aqueous Phase Preparation:** Soya lecithin and Tween 80 were dissolved in 10.0 mL of double-distilled water and heated to 75°C to match the temperature of the lipid phase.
3. **Primary Emulsification:** The heated aqueous phase was added dropwise to the molten lipid phase under continuous stirring. The mixture was homogenized using a high-speed ultrahomogenizer (Heidolph, Germany) at 12,000 rpm for 12 minutes at 75 °C to produce a coarse oil-in-water microemulsion.
4. **Ultrasonication:** The resulting hot emulsion was subjected to probe ultrasonication (Sonics, USA) at 60% amplitude for 6 minutes (30 seconds pulse ON / 30 seconds pulse OFF) in a temperature-controlled bath to minimize thermal degradation.
5. **Cooling and Nanoparticle Formation:** The nanoemulsion was cooled gradually to room temperature under gentle stirring, prompting lipid recrystallization and the formation of solid lipid nanoparticles.

### Characterization of Dapsone Solid Lipid Nanoparticles

#### Dynamic Light Scattering (Particle Size, Polydispersity Index, and Zeta Potential)

Mean hydrodynamic diameter (Z-average) and polydispersity index (PDI) were determined via dynamic light scattering (DLS) using a Malvern Zetasizer Nano ZS (Malvern Instruments, UK) at 25.0±0.1°C. Samples were diluted 1:100 with double-distilled water prior to analysis to maintain suitable light-scattering intensity. Zeta potential was determined by electrophoretic light scattering using disposable folded capillary cells.

#### Entrapment Efficiency (% EE)

The entrapment efficiency of DDP-SLN formulations was evaluated using ultracentrifugation. A 5.0 mL volume of the SLN dispersion was transferred into a centrifuge cell and spun at 15,000 rpm for 35 minutes at 4°C using a refrigerated centrifuge. The untrapped (free) Dapsone present in the supernatant was collected, diluted with phosphate buffer (pH 6.8), and quantified spectrophotometrically at  $\lambda_{\text{max}} = 295 \text{ nm}$ . The percentage entrapment efficiency was calculated using the following equation:

$$\% \text{ EE} = \frac{\text{Total Mass of Dapsone Added} - \text{Mass of Free Dapsone in}}{\text{Total Mass of Dapsone Added}}$$

### ***Scanning Electron Microscopy (SEM)***

Morphological characterization of the optimized DDP-SLN was evaluated using scanning electron microscopy (Hitachi SU 3500, Japan). A droplet of diluted nanoparticle dispersion was applied to a carbon-adhesive tape mounted on an aluminum stub, air-dried, and sputter-coated with a thin gold-palladium layer under vacuum. Imaging was conducted at an accelerating voltage of 10 kV.

### **Preparation of Dapsone SLN-Loaded Polymeric Hydrogel**

The optimized DDP-SLN dispersion was incorporated into a cross-linked Carbopol 934 gel matrix:

1. **Hydrogel Preparation:** Carbopol 934 (0.1 g, 1.0% w/w) was sprinkled evenly into 2.0 mL of double-distilled water containing Propylene glycol (0.5 g) and Glycerol (0.5 g). The mixture was left to hydrate overnight.
2. **SLN Incorporation:** The optimized DDP-SLN dispersion (10.0 mL, containing 10.0 mg Dapsone equivalent) was added in small portions to the hydrated polymer dispersion under constant, gentle stirring to prevent air entrapment.
3. **Neutralization and Gelation:** Triethanolamine was added dropwise with gentle mixing until a transparent gel formed, adjusting the final pH to 5.5–6.5. The formulation weight was adjusted to 10.0 g with distilled water, followed by deaeration for 2 hours.

### **Characterization of DDP-SLN Polymeric Hydrogel**

#### **Organoleptic Evaluation**

The hydrogel was visually inspected for clarity, color, homogeneity, phase separation, and presence of foreign matter or grittiness.

#### **Determination of pH**

The pH of the hydrogel was evaluated using a calibrated digital pH meter (LT Lutron, Taiwan). Briefly, 1.0 g of the hydrogel was dispersed in 100.0 mL of neutral distilled water, allowed to equilibrate for 2 hours, and measured in triplicate at  $25 \pm 1$  °C.

#### **Rheological Viscosity Evaluation**

Viscosity measurements were conducted using a Brookfield DV-E rotational viscometer equipped with spindle number 4. Analysis was performed on 50.0 g of hydrogel at 20 rpm at  $25 \pm 0.5$  °C.

#### **Spreadability Measurement**

$$S = \frac{m \cdot l}{t}$$

Spreadability was evaluated using two glass plates mounted on a dedicated test assembly. One gram of hydrogel was placed within a 1.0 cm<sup>2</sup> circle marked on the lower plate. The upper glass plate was placed over the sample, and a 1000 g weight was applied for 5 minutes to achieve a uniform gel film. A 70 g weight was attached to the upper slide, and the time required for the top slide to slip off a distance of 6.0 cm was recorded. Spreadability was calculated as follows:

Where S is spreadability (g·cm/s), m is the weight tied to the upper slide (70 g), l is the glass slide length (6.0 cm), and t is the elapsed time (seconds).

### In Vitro Release Studies and Kinetics

In vitro release studies were performed using a Franz diffusion cell apparatus across a synthetic dialysis membrane (MWCO: 12,000–14,000 Da). The receptor compartment (22.0 mL volume) was filled with phosphate buffer solution (pH 6.8) containing 0.5% v/v Tween 80 to preserve sink conditions. The medium was stirred at 100 rpm and maintained at 37±0.5°C.

The pre-hydrated dialysis membrane was clamped between the donor and receptor compartments. An aliquot of 2.0 mL of SLN dispersion (or 1.0 g of DDP-SLN hydrogel) was loaded into the donor chamber. At designated time intervals (0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours), 2.0 mL samples were withdrawn from the receptor chamber and replaced with an equal volume of fresh buffer. Dapsone content was quantified spectrophotometrically at  $\lambda_{\text{max}} = 295 \text{ nm}$ . Cumulative percentage drug release (% CDR) was plotted as a function of time.

Release profiles of the optimized formulation were fitted to mathematical models to evaluate release kinetics:

1. Zero-Order Model:  $Q_t = Q_0 + K_0 t$
2. First-Order Model:  $\ln Q_t = \ln Q_0 - K_1 t$
3. Higuchi Diffusion Model:  $Q_t = K_H \cdot t^{1/2}$
4. Korsmeyer-Peppas Model:  $M_t / M_\infty = K_P \cdot t^n$

Where  $Q_t$  is the amount of drug released at time  $t$ ;  $Q_0$  is initial drug concentration;  $K_0$ ,  $K_1$ ,  $K_H$ ,  $K_P$  are release rate constants; and  $n$  is the diffusional exponent indicating the transport mechanism ( $n \leq 0.45$  for Fickian diffusion;  $0.45 < n < 0.89$  for non-Fickian anomalous transport;  $n \geq 0.89$  for Case II transport).

### Stability Analysis

Stability testing was conducted in accordance with ICH guidelines (Q1A R2). Samples of the optimized DDP-SLN hydrogel were packaged in aluminum collapsible tubes and stored under two environmental conditions:

- Standard Room Temperature (25±2°C / 60±5% RH) for 6 months.

- Accelerated Conditions ( $40\pm 2^{\circ}\text{C}$  /  $75\pm 5\%$  RH) for 6 months.

Assays were performed at 0, 1, 3, and 6 months to monitor changes in physical appearance, pH, viscosity, spreadability, drug entrapment efficiency, and drug release profiles.

## RESULTS AND DISCUSSION

### Preformulation and Spectral Analysis

Determinations of Dapsone's melting point yielded a mean value of  $183.0^{\circ}\text{C}$  (range  $182\text{--}184^{\circ}\text{C}$ ), consistent with standard literature values ( $183\text{--}185^{\circ}\text{C}$ ), confirming drug purity. UV spectrophotometric analysis in phosphate buffer (pH 6.8) generated an absorption peak at  $\lambda_{\text{max}} = 295\text{ nm}$ . The standard calibration curve showed linearity across the concentration range of 2.0 to  $12.0\text{ }\mu\text{g/mL}$ , represented by the regression equation  $y = 0.0353x + 0.0896$  with a coefficient of determination ( $R^2$ ) of 0.9974.

**Table 3: Infrared spectral peaks and functional group assignments for Dapsone, excipients, and formulation mixture**

| Compound / Sample              | Functional Group Assignment         | Standard Literature Wavenumber( $\text{cm}^{-1}$ ) | Observed Wavenumber( $\text{cm}^{-1}$ ) |
|--------------------------------|-------------------------------------|----------------------------------------------------|-----------------------------------------|
| Pure Dapsone                   | N–H stretching (Primary Amine)      | 3500–3300                                          | 3383, 3271                              |
|                                | C–H stretching (Aromatic)           | 3100–3000                                          | 3063                                    |
|                                | S=O stretching (Asymmetric Sulfone) | 1350–1280                                          | 1280                                    |
|                                | S=O stretching (Symmetric Sulfone)  | 1160–1130                                          | 1142                                    |
|                                | C–N stretching (Aromatic Amine)     | 1350–1250                                          | 1226                                    |
|                                | C=C stretching (Aromatic Ring)      | 1600–1450                                          | 1593, 1492                              |
|                                | O–H stretching                      | 3600–3200                                          | 3313                                    |
| Glyceryl monostearate (GMS)    | C–H stretching (Aliphatic)          | 2950–2850                                          | 2916, 2850                              |
|                                | C=O stretching (Ester)              | 1750–1730                                          | 1730                                    |
| Soya Lecithin                  | C–H stretching (Aliphatic)          | 3000–2850                                          | 2924, 2857                              |
|                                | P=O stretching (Phosphate Ester)    | 1250–1200                                          | 1230                                    |
| Tween 80                       | O–H stretching                      | 3600–3200                                          | 3450                                    |
|                                | C=O stretching (Ester)              | 1750–1735                                          | 1735                                    |
| Physical Mixture / Formulation | N–H stretching (Dapsone Amine)      | 3500–3300                                          | 3356, 3242                              |
|                                | C–H stretching (Aliphatic)          | 2950–2850                                          | 2918, 2854                              |
|                                | C=O stretching (Ester)              | 1750–1700                                          | 1730                                    |
|                                | S=O stretching (Sulfone)            | 1350–1130                                          | 1280, 1136                              |

FTIR spectrum analysis of pure Dapsone confirmed its characteristic molecular features: dual N–H

stretching doublets at 3383  $\text{cm}^{-1}$  and 3271  $\text{cm}^{-1}$ , an asymmetric sulfone (S=O) band at 1280  $\text{cm}^{-1}$ , a symmetric sulfone peak at 1142  $\text{cm}^{-1}$ , and aromatic ring vibrations (C=C) at 1593  $\text{cm}^{-1}$ . As outlined in Table 3, the spectra of the physical mixture retained the characteristic drug absorption bands without significant shifts or attenuation, indicating chemical compatibility between Dapsone and the lipid/surfactant components.

### Evaluation and Optimization of DDP-SLN Formulations

The 17 DDP-SLN formulations prepared according to the Box-Behnken design were characterized for Particle Size ( $Y_1$ ), Entrapment Efficiency ( $Y_2$ ), and Cumulative Percentage Drug Release at 12 hours ( $Y_3$ ). Experimental outputs for all runs are provided in Table 4.

**Table 4: Experimental responses obtained for Box-Behnken Design runs (F1–F17)**

| Run Code | Factor 1: GMS (A,mg) | Factor 2: Soya Lecithin (B, mg) | Factor 3: Tween 80 (C, mg) | Y1: Particle Size (nm) | Y2: Entrapment Efficiency (%) | Y3: % CDR at 12 h(%) |
|----------|----------------------|---------------------------------|----------------------------|------------------------|-------------------------------|----------------------|
| F1       | 300                  | 150                             | 150                        | 155.05                 | 87.94                         | 87.39                |
| F2       | 400                  | 200                             | 150                        | 185.04                 | 84.23                         | 86.87                |
| F3       | 200                  | 200                             | 150                        | 146.84                 | 90.14                         | 78.99                |
| F4       | 300                  | 200                             | 200                        | 165.23                 | 85.97                         | 81.92                |
| F5       | 400                  | 150                             | 150                        | 179.55                 | 86.04                         | 87.96                |
| F6       | 300                  | 150                             | 100                        | 154.21                 | 88.15                         | 87.44                |
| F7       | 400                  | 150                             | 150                        | 166.85                 | 80.08                         | 86.51                |
| F8       | 400                  | 100                             | 150                        | 164.92                 | 83.00                         | 88.01                |
| F9       | 300                  | 150                             | 200                        | 156.92                 | 87.75                         | 87.41                |
| F10      | 300                  | 100                             | 200                        | 157.23                 | 86.75                         | 90.01                |
| F11      | 300                  | 200                             | 100                        | 176.35                 | 88.25                         | 83.90                |
| F12      | 200                  | 150                             | 150                        | 133.86                 | 85.57                         | 78.38                |
| F13      | 300                  | 150                             | 150                        | 156.02                 | 88.26                         | 87.21                |
| F14      | 300                  | 150                             | 150                        | 154.80                 | 87.97                         | 87.77                |
| F15      | 200                  | 150                             | 200                        | 139.43                 | 88.17                         | 85.54                |
| F16      | 300                  | 100                             | 100                        | 148.68                 | 81.35                         | 84.20                |
| F17      | 200                  | 100                             | 150                        | 132.68                 | 85.20                         | 85.89                |

### ANOVA Analysis for Particle Size ( $Y_1$ )

Particle sizes ranged from 132.68 nm (F17) to 185.04 nm (F2). Analysis of variance (ANOVA) indicated that the quadratic model was statistically significant ( $p < 0.0001$ , F-value = 42.18) with a high coefficient of determination ( $R^2 = 0.9819$ ). The final polynomial equation expressed in coded terms is:

$$Y_1 = 155.37 + 18.24A + 4.96B + 1.18C + 4.19AB + 2.89AC - 6.70BC + 1.28A^2 + 5.12B^2 - 1.84C^2$$

Increasing Glyceryl monostearate concentration (A) produced a significant increase in particle dimensions ( $p < 0.0001$ ), attributable to increased lipid phase viscosity, reduced homogenization

efficiency, and particle coalescence during cooling. Conversely, elevated surfactant levels reduced particle size by lowering interfacial tension at the oil-water interface.

### ANOVA Analysis for Entrapment Efficiency ( $Y_2$ )

Entrapment efficiency ranged from 80.08% (F7) to 90.14% (F3). The fitted quadratic model showed statistical significance ( $p = 0.0003$ ,  $R^2 = 0.9654$ ), yielding the following equation:

$$Y_2 = 88.04 - 1.62A + 1.85B + 1.11C + 0.91AB + 2.59AC - 2.25BC - 3.42A^2 - 1.08B^2 - 0.44C^2$$

Higher lipid concentrations provided a larger hydrophobic core volume, accommodating greater quantities of the lipophilic Dapsone molecule. Increasing Soya lecithin (B) and Tween 80 (C) concentrations also supported drug retention within the lipid core by providing surfactant coating at the interface.

### ANOVA Analysis for Cumulative Percentage Drug Release ( $Y_3$ )

Percentage cumulative drug release at 12 hours ranged between 78.38% (F12) and 90.01% (F10).

The quadratic model equation for response  $Y_3$  is:

$$Y_3 = 87.56 + 2.94A - 0.88B + 1.84C + 1.00AB - 1.23AC + 1.02BC - 2.97A^2 - 2.81B^2 + 0.18C^2$$

Model optimization identified optimal formulation parameters: Glyceryl monostearate at 245.82 mg, Soya lecithin at 148.64 mg, and Tween 80 at 162.31 mg. The predicted values were: Particle Size = 141.12 nm, Entrapment Efficiency = 88.10%, and % CDR = 87.65%.

Validation experiments performed on the optimized formulation produced experimental values closely matching the model predictions: mean particle size of 140.38 nm, entrapment efficiency of 87.93%, and cumulative drug release of 87.90%.

### Physicochemical Characterization of Optimized DDP-SLN and Hydrogel

Dynamic light scattering analysis of the optimized DDP-SLN dispersion showed a mean hydrodynamic diameter of 140.38 nm with a polydispersity index of 0.287, confirming a narrow particle size distribution. The zeta potential was -35.0 mV, indicating sufficient electrostatic repulsion to prevent nanoparticle aggregation during storage.

**Table 5: Physicochemical properties of the optimized DDP-SLN dispersion and hydrogel**

| Parameter                  | Optimized DDP-SLN Dispersion | Optimized DDP-SLN Polymeric Hydrogel |
|----------------------------|------------------------------|--------------------------------------|
| Visual Appearance          | Translucent milky dispersion | Smooth, clear, homogeneous gel       |
| Mean Particle Size (nm)    | 140.38 ± 1.25                | Not Applicable                       |
| Polydispersity Index (PDI) | 0.287 ± 0.012                | Not Applicable                       |
| Zeta Potential (mV)        | -35.0 ± 0.82                 | Not Applicable                       |
| Entrapment Efficiency(%)   | 87.93 ± 0.64                 | Not Applicable                       |
| pH Value                   | 6.12 ± 0.05                  | 6.23 ± 0.08                          |
| Viscosity at 20 rpm (cP)   | Not Applicable               | 8486.67 ± 70.95                      |

|                        |                |              |
|------------------------|----------------|--------------|
| Spreadability (g·cm/s) | Not Applicable | 18.42 ± 0.35 |
| Drug Content (%)       | 98.85 ± 0.42   | 98.12 ± 0.50 |

Scanning Electron Microscopy (SEM) confirmed that the nanoparticles exhibited a spherical morphology with uniform spatial distribution and minimal aggregation.

The optimized DDP-SLN dispersion was incorporated into a 1.0% w/w Carbopol 934 gel. The resulting hydrogel was smooth, homogeneous, and free of phase separation or grittiness. As summarized in Table 5, the hydrogel exhibited an average surface pH of 6.23±0.08, suitable for skin application. Rheological evaluation yielded a viscosity of 8486.67±70.95 cP at 20 rpm, providing suitable flow resistance and spreadability (18.42 g·cm/s).

### ***In Vitro* Drug Release Kinetics**

Comparative in vitro dissolution profiles for formulations F1–F17 and the optimized DDP-SLN hydrogel are illustrated across intervals in Table 6.

**Table 6: In vitro percentage cumulative drug release profiles of formulations F1–F17.**

| Formulation | 0.5 h | 1 h   | 2 h  | 3 h  | 4 h  | 8 h  | 10 h | 12 h  |
|-------------|-------|-------|------|------|------|------|------|-------|
| F1          | 16.8  | 25.9  | 39.5 | 47.9 | 51.6 | 71.3 | 79.8 | 87.39 |
| F2          | 12.8  | 20.05 | 35.5 | 49.5 | 53.6 | 72.7 | 78.3 | 86.87 |
| F3          | 13.5  | 18.6  | 25.9 | 37.9 | 54.3 | 64.3 | 69.3 | 78.99 |
| F4          | 10.5  | 17.5  | 23.6 | 31.4 | 49.5 | 69.3 | 72.3 | 81.92 |
| F5          | 15.4  | 26.5  | 39.5 | 41.7 | 53.9 | 65.8 | 79.8 | 87.96 |
| F6          | 9.85  | 17.4  | 29.3 | 40.3 | 64.8 | 72.8 | 77.9 | 87.44 |
| F7          | 10.8  | 18.4  | 28.4 | 41.6 | 51.5 | 65.6 | 79.8 | 86.51 |
| F8          | 12.5  | 22.5  | 27.5 | 43.5 | 55.5 | 63.9 | 76.4 | 88.01 |
| F9          | 15.8  | 25.6  | 31.3 | 39.6 | 61.8 | 77.5 | 81.6 | 87.41 |
| F10         | 18.8  | 23.8  | 29.3 | 45.9 | 69.4 | 75.5 | 83.7 | 90.01 |
| F11         | 12.5  | 21.8  | 33.4 | 39.8 | 53.8 | 65.3 | 78.3 | 83.9  |
| F12         | 10.3  | 19.8  | 28.5 | 35.6 | 61.7 | 68.4 | 71.5 | 78.38 |
| F13         | 15.6  | 20.3  | 27.3 | 40.3 | 55.4 | 61.8 | 73.8 | 87.21 |
| F14         | 12.8  | 17.7  | 30.5 | 45.5 | 54.8 | 69.4 | 75.6 | 87.77 |
| F15         | 9.1   | 16.3  | 25.0 | 36.1 | 46.6 | 67.8 | 72.5 | 85.54 |
| F16         | 17.7  | 21.6  | 29.5 | 39.5 | 43.8 | 65.8 | 71.5 | 84.2  |
| F17         | 10.5  | 18.6  | 26.7 | 41.8 | 51.8 | 63.8 | 74.8 | 87.93 |

The release profile displayed a biphasic pattern: an initial rapid drug release over the first 2 hours, attributed to untrapped Dapsone at the nanoparticle outer lipid shell, followed by a sustained release phase up to 12 hours driven by drug diffusion through the core matrix.

Mathematical fitting of release data for the optimized formulation yielded linear regression values ( $R^2$ ) across kinetic models: Zero-order ( $R^2 = 0.9245$ ), First-order ( $R^2 = 0.9612$ ), Higuchi model ( $R^2 = 0.9910$ ), and Korsmeyer-Peppas model ( $R^2 = 0.9884$ ,  $n = 0.612$ ). The Higuchi model produced the highest correlation coefficient, indicating that drug release from the lipid matrix is diffusion-

controlled. The release exponent  $n = 0.612$  ( $0.45 < n < 0.89$ ) indicates a non-Fickian (anomalous) transport mechanism, combining lipid matrix erosion with drug diffusion.

### Stability Studies

Stability evaluation of the optimized DDP-SLN hydrogel stored under standard ( $25 \pm 2^\circ\text{C}$  /  $60 \pm 5\%$  RH) and accelerated conditions ( $40 \pm 2^\circ\text{C}$  /  $75 \pm 5\%$  RH) over 6 months showed no significant changes in appearance, pH, or spreadability, as shown in Table 7

**Table 7: Stability parameters of optimized DDP-SLN polymeric hydrogel over 6 months**

| Storage Condition | Time Interval | Physical Appearance    | pH              | Viscosity at 20 rpm(cP) | Entrapment Efficiency (%) | Drug Content (%)  |
|-------------------|---------------|------------------------|-----------------|-------------------------|---------------------------|-------------------|
| Initial           | 0 months      | Clear, Homogeneous gel | $6.23 \pm 0.08$ | $8486.67 \pm 70.95$     | $87.93 \pm 0.64$          | $98.12 \pm 0.50$  |
| 250C/60% RH       | 1 Month       | Unchanged              | $6.22 \pm 0.06$ | $8480.00 \pm 65.00$     | $87.85 \pm 65.00$         | $98.05 \pm 65.00$ |
|                   | 3 Month       | Unchanged              | $6.20 \pm 0.07$ | $8472.33 \pm 68.20$     | $87.62 \pm 0.61$          | $97.88 \pm 0.52$  |
|                   | 6 Months      | Unchanged              | $6.18 \pm 0.05$ | $8460.00 \pm 72.10$     | $87.20 \pm 0.55$          | $97.50 \pm 0.48$  |
| 400C/75% RH       | 1 Months      | Unchanged              | $6.21 \pm 0.07$ | $8465.00 \pm 75.00$     | $87.40 \pm 0.60$          | $97.80 \pm 0.40$  |
|                   | 3 Months      | Unchanged              | $6.16 \pm 0.08$ | $8430.00 \pm 80.50$     | $86.85 \pm 0.70$          | $97.15 \pm 0.55$  |
|                   | 6 Months      | Slight viscosity drop  | $6.10 \pm 0.09$ | $8385.00 \pm 85.00$     | $86.10 \pm 0.68$          | $96.40 \pm 0.62$  |

Under accelerated conditions, a minor reduction in viscosity (8385.00 cP) and entrapment efficiency (86.10%) was observed at 6 months, likely due to elevated kinetic energy causing minor lipid softening. However, all measured parameters remained within acceptable limits, confirming formulation stability.

### CONCLUSION

A Dapsone-loaded solid lipid nanoparticle polymeric hydrogel was developed and optimized using a Box-Behnken design. The optimized SLN formulation composed of Glyceryl monostearate, Soya lecithin, and Tween 80 produced nanometer-sized particles (140.38 nm) with high entrapment efficiency (87.93%) and a negative zeta potential (-35.0 mV). Incorporation into a Carbopol 934 hydrogel matrix yielded suitable rheological properties, spreadability, and a skin-compatible pH (6.23). Drug release followed Higuchi diffusion kinetics via non-Fickian anomalous transport over 12 hours. Stability studies over 6 months confirmed physical and chemical integrity. The developed DDP-SLN hydrogel offers a stable nanostructured carrier system for the localized delivery of Dapsone.

## Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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