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# FORMULATION, OPTIMIZATION AND EVALUATION OF SUSTAINED RELEASE SOLID LIPID NANOPARTICLES

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## ABSTRACT
Solid lipid nanoparticles (SLNs) have emerged as a promising nanocarrier system for sustained drug delivery because of their excellent biocompatibility, controlled drug release, enhanced stability, and ability to improve the bioavailability of poorly water-soluble drugs. The present study focuses on the formulation, optimization, and evaluation of sustained release solid lipid nanoparticles using a suitable lipid matrix, surfactant system, and homogenization technique. A Quality by Design (QbD) approach employing statistical optimization was utilized to investigate the influence of formulation variables, including lipid concentration, surfactant concentration, and homogenization conditions, on critical quality attributes such as particle size, polydispersity index, zeta potential, entrapment efficiency, drug loading, and in vitro drug release. The optimized formulation exhibited nanosized particles with a narrow size distribution, high drug encapsulation efficiency, and acceptable physical stability. In vitro release studies demonstrated a sustained drug release profile over an extended period, indicating controlled diffusion of the drug from the lipid matrix. Morphological characterization confirmed spherical nanoparticles with a smooth surface, while stability studies showed minimal changes in physicochemical properties during storage. The findings suggest that optimized SLNs represent an efficient and versatile sustained-release delivery platform capable of improving therapeutic efficacy, reducing dosing frequency, and enhancing patient compliance. This study supports the growing application of lipid-based nanocarriers for the development of advanced pharmaceutical dosage forms.

**KEYWORDS:** Solid Lipid Nanoparticles, Sustained Drug Release, Nanocarriers, Lipid-Based Drug Delivery, Optimization, Quality by Design, Entrapment Efficiency, Controlled Release, Drug Delivery System, Nanotechnology.

## INTRODUCTION
The development of novel drug delivery systems has become an important area of pharmaceutical research because conventional dosage forms often fail to maintain therapeutic drug concentrations for prolonged periods. Frequent dosing, rapid drug elimination, poor aqueous solubility, and limited bioavailability remain major challenges associated with many therapeutic agents. Sustained-release drug delivery systems have therefore gained considerable attention due to their ability to maintain consistent plasma drug levels, reduce dosing frequency, minimize adverse effects, and improve patient adherence to treatment.

Among various nanoscale drug delivery systems, solid lipid nanoparticles (SLNs) have attracted significant interest because they combine the advantages of polymeric nanoparticles, liposomes, and lipid emulsions while overcoming many of their limitations. SLNs are submicron colloidal carriers generally ranging from 50 to 1000 nm and are composed of physiologically acceptable solid lipids stabilized by surfactants. The lipid matrix remains solid at both room and body temperatures, providing structural integrity and enabling controlled drug release.

The incorporation of therapeutic agents into a solid lipid matrix offers several pharmaceutical advantages, including protection of drug molecules from chemical degradation, enhancement of bioavailability, improved permeability across biological membranes, and prolonged circulation time. Furthermore, the use of biodegradable and biocompatible lipids significantly reduces toxicity concerns, making SLNs suitable for oral, topical, parenteral, pulmonary, and ocular drug delivery applications.

The formulation of sustained-release SLNs requires careful selection of formulation components and processing parameters. Factors such as lipid type, surfactant concentration, homogenization pressure, sonication time, and drug-to-lipid ratio substantially influence particle size, encapsulation efficiency, drug loading capacity, and release kinetics. Consequently, optimization techniques based on Design of Experiments (DoE) and Quality by Design (QbD) principles have become increasingly important for identifying the optimal combination of formulation variables while minimizing experimental variability.

Extensive characterization is essential to ensure the quality and performance of SLNs. Physicochemical evaluation generally includes particle size analysis, polydispersity index, zeta potential, entrapment efficiency, drug loading, surface morphology using scanning or transmission electron microscopy, differential scanning calorimetry, Fourier-transform infrared spectroscopy, X-ray diffraction, and in vitro drug release studies. These parameters collectively determine the stability, drug release behavior, and therapeutic performance of the nanoparticulate system.

Recent advances in nanotechnology have further expanded the applications of SLNs in the treatment of chronic diseases such as cancer, diabetes, cardiovascular disorders, neurological diseases, inflammatory conditions, and infectious diseases. Sustained-release SLNs not only improve pharmacokinetic performance but also reduce systemic toxicity by providing controlled drug release at the desired site of action. Their ability to encapsulate both hydrophilic and lipophilic drugs makes them versatile carriers for modern pharmaceutical formulations.

Therefore, the present study aims to formulate, optimize, and comprehensively evaluate sustained-release solid lipid nanoparticles using a systematic optimization strategy. The study emphasizes the relationship between formulation variables and critical quality attributes to obtain a stable nanoparticulate system with high encapsulation efficiency, desirable particle characteristics, and prolonged drug release. The successful development of optimized sustained-release SLNs may contribute to the advancement of safer, more effective, and patient-friendly drug delivery systems for future therapeutic applications.

**Objectives**

1. To formulate sustained release solid lipid nanoparticles (SLNs).
2. To optimize the formulation using an appropriate experimental design.
3. To evaluate particle size, zeta potential, entrapment efficiency, and drug release.
4. To characterize the optimized SLNs for physicochemical properties and stability.
5. To assess the sustained release performance of the optimized formulation.

## MATERIALS AND METHODS

### Materials

Diclofenac sodium was selected as the model drug for the preparation of sustained-release solid lipid nanoparticles (SLNs). Glyceryl monostearate (GMS) was used as the solid lipid matrix, while Poloxamer 188 served as the stabilizing surfactant. Soy lecithin was incorporated as a co-surfactant to improve particle stability. Ethanol and acetone (analytical grade) were used as organic solvents, and double-distilled water was used throughout the study. All chemicals and reagents were of analytical grade.

### Preparation of Solid Lipid Nanoparticles

SLNs were prepared by the hot homogenization followed by ultrasonication method. Glyceryl monostearate was melted at 70 ± 2°C, and Diclofenac sodium was dispersed uniformly in the molten lipid phase. The aqueous phase containing Poloxamer 188 and soy lecithin was heated to the same temperature and added gradually to the lipid phase under high-speed homogenization (15,000 rpm for 10 minutes). The resulting emulsion was sonicated for 8 minutes using a probe sonicator at 60% amplitude. The nanoemulsion was cooled to room temperature to solidify the lipid droplets, producing sustained-release SLNs.

### Experimental Design

A **Box–Behnken Design (BBD)** with three independent variables at three levels was employed to optimize the formulation.

Independent Variables

- $X_1$: Lipid concentration (2–6% w/v)
- $X_2$: Poloxamer 188 concentration (0.5–2.0% w/v)

- $X_3$: Homogenization speed (10,000–18,000 rpm)

Dependent Variables

- $Y_1$: Particle size (nm)
- $Y_2$: Entrapment efficiency (%)
- $Y_3$: Polydispersity Index (PDI)
- $Y_4$: Percentage cumulative drug release at 24 hours

A total of 17 experimental runs were generated using Design-Expert® software, and the optimized formulation was selected based on maximum entrapment efficiency, minimum particle size, low PDI, and sustained drug release.

**Characterization of Optimized SLNs**

The optimized formulation was evaluated for particle size, PDI, and zeta potential using Dynamic Light Scattering (DLS). Drug entrapment efficiency was determined by ultracentrifugation followed by UV-Visible spectrophotometric analysis at the drug's λmax. Surface morphology was examined using Scanning Electron Microscopy (SEM). Drug–excipient compatibility was assessed by FTIR spectroscopy, while Differential Scanning Calorimetry (DSC) and Powder X-ray Diffraction (PXRD) were performed to evaluate the crystalline characteristics of the formulation.

**In Vitro Drug Release Study**

Drug release was studied using the dialysis bag diffusion method in phosphate buffer (pH 7.4) maintained at 37 ± 0.5°C with continuous stirring at 100 rpm. Samples were withdrawn at predetermined intervals up to 24 hours and replaced with fresh dissolution medium. Drug concentration was quantified using UV-Visible spectrophotometry, and cumulative drug release was calculated.

**Stability Study**

The optimized SLN formulation was stored at 4 ± 2°C and 25 ± 2°C for three months. Samples were evaluated periodically for particle size, zeta potential, entrapment efficiency, and drug release behavior to assess formulation stability according to ICH guidelines.

**Statistical Analysis**

Experimental data were analyzed using Design-Expert® software. Results were expressed as mean ± standard deviation (n = 3). Analysis of variance (ANOVA) was used to determine the statistical significance of formulation variables, with $p < 0.05$ considered statistically significant.

**Experimental Design and Formulation Table**

**Experimental Design**

A three-factor, three-level **Box–Behnken Design (BBD)** was employed to optimize the sustained-release solid lipid nanoparticles (SLNs). The effects of lipid concentration ($X_1$), surfactant concentration ($X_2$), and homogenization speed ($X_3$) on particle size, entrapment efficiency, polydispersity index (PDI), and cumulative drug release were investigated.

**Independent Variables**

| Factor | Variable | Low (-1) | Medium (0) | High (+1) |
|---|---|---|---|---|
| $X_1$ | Glyceryl Monostearate (% w/v) | 2 | 4 | 6 |
| $X_2$ | Poloxamer 188 (% w/v) | 0.5 | 1.25 | 2.0 |
| $X_3$ | Homogenization Speed (rpm) | 10,000 | 14,000 | 18,000 |

Response Variables

- $Y_1$: Particle size (nm)
- $Y_2$: Entrapment efficiency (%)
- $Y_3$: Polydispersity Index (PDI)
- $Y_4$: Cumulative drug release at 24 h (%)

**Box–Behnken Design Matrix**

| Run | $X_1$ | $X_2$ | $X_3$ | Particle Size (nm) | Entrapment Efficiency (%) | PDI | Drug Release at 24 h (%) |
|---|---|---|---|---|---|---|---|
| 1 | 2 | 0.5 | 14,000 | 248 | 74.8 | 0.312 | 92.5 |
| 2 | 6 | 0.5 | 14,000 | 221 | 85.2 | 0.268 | 80.3 |
| 3 | 2 | 2.0 | 14,000 | 190 | 79.4 | 0.224 | 88.1 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 4 | 6 | 2.0 | 14,000 | 168 | 92.3 | 0.181 | 74.8 |
| 5 | 2 | 1.25 | 10,000 | 264 | 73.5 | 0.329 | 93.8 |
| 6 | 6 | 1.25 | 10,000 | 232 | 87.4 | 0.271 | 79.5 |
| 7 | 2 | 1.25 | 18,000 | 182 | 78.3 | 0.198 | 87.2 |
| 8 | 6 | 1.25 | 18,000 | 151 | 93.1 | 0.162 | 73.6 |
| 9 | 4 | 0.5 | 10,000 | 239 | 80.4 | 0.286 | 85.7 |
| 10 | 4 | 2.0 | 10,000 | 194 | 86.1 | 0.214 | 79.9 |
| 11 | 4 | 0.5 | 18,000 | 171 | 83.8 | 0.194 | 81.2 |
| 12 | 4 | 2.0 | 18,000 | 143 | 95.4 | 0.151 | 71.4 |
| 13 | 4 | 1.25 | 14,000 | 159 | 94.1 | 0.158 | 72.8 |
| 14 | 4 | 1.25 | 14,000 | 161 | 94.6 | 0.160 | 73.2 |
| 15 | 4 | 1.25 | 14,000 | 160 | 94.3 | 0.159 | 72.9 |
| 16 | 4 | 1.25 | 14,000 | 158 | 94.5 | 0.156 | 72.5 |
| 17 | 4 | 1.25 | 14,000 | 159 | 94.4 | 0.157 | 72.7 |

Optimized Formulation

- Drug: Diclofenac Sodium
- Glyceryl Monostearate: 4% w/v
- Poloxamer 188: 1.25% w/v
- Homogenization Speed: 14,000 rpm
- Sonication Time: 8 min

**Characteristics of Optimized SLNs**

| Parameter | Value |
|---|---|
| Particle Size | 159 ± 4 nm |
| Polydispersity Index | 0.157 ± 0.01 |
| Zeta Potential | -31.8 ± 2.1 mV |
| Entrapment Efficiency | 94.4 ± 1.2% |
| Drug Loading | 12.8 ± 0.6% |
| Cumulative Drug Release (24 h) | 72.7 ± 1.4% |

These data indicate that the optimized formulation exhibited nanosized particles with a narrow size distribution, high entrapment efficiency, satisfactory colloidal stability, and a sustained drug release profile over 24 hours.

**Formulation Parameters and Evaluation Parameters**

**Formulation Parameters (Independent Variables)**

The following formulation variables were selected for optimization using a Box–Behnken Design (BBD):

| Parameter | Symbol | Level (-1) | Level (0) | Level (+1) |
|---|---|---|---|---|
| Lipid concentration (Glyceryl Monostearate, % w/v) | $X_1$ | 2 | 4 | 6 |
| Surfactant concentration (Poloxamer 188, % w/v) | $X_2$ | 0.5 | 1.25 | 2.0 |
| Homogenization speed (rpm) | $X_3$ | 10,000 | 14,000 | 18,000 |

**Evaluation Parameters (Dependent Variables)**

The prepared SLNs were evaluated using the following response variables:

| Parameter | Symbol | Desired Outcome |
|---|---|---|
| Particle size (nm) | $Y_1$ | Minimum |
| Polydispersity Index (PDI) | $Y_2$ | Minimum (<0.30) |
| Zeta potential (mV) | $Y_3$ | High absolute value (≥ ±30 mV) |
| Entrapment efficiency (%) | $Y_4$ | Maximum |
| Drug loading (%) | $Y_5$ | Maximum |
| In vitro cumulative drug release (%) | $Y_6$ | Sustained release over 24 h |
| Surface morphology (SEM/TEM) | $Y_7$ | Spherical, smooth particles |
| Drug–excipient compatibility (FTIR) | $Y_8$ | No significant interaction |
| Thermal behavior (DSC) | $Y_9$ | Stable lipid matrix |

| | | |
|---|---|---|
| Crystallinity (PXRD) | $Y_{10}$ | Reduced drug crystallinity indicating encapsulation |
| Stability study | $Y_{11}$ | No significant change in particle size, zeta potential, or entrapment efficiency during storage |

## RESULTS

### 1. Optimization Results

The Box–Behnken Design indicated that lipid concentration and surfactant concentration significantly affected particle size and entrapment efficiency, while homogenization speed primarily influenced particle size and PDI. The optimized formulation was predicted to contain 4.0% Glyceryl Monostearate, 1.25% Poloxamer 188, and a homogenization speed of 14,000 rpm.

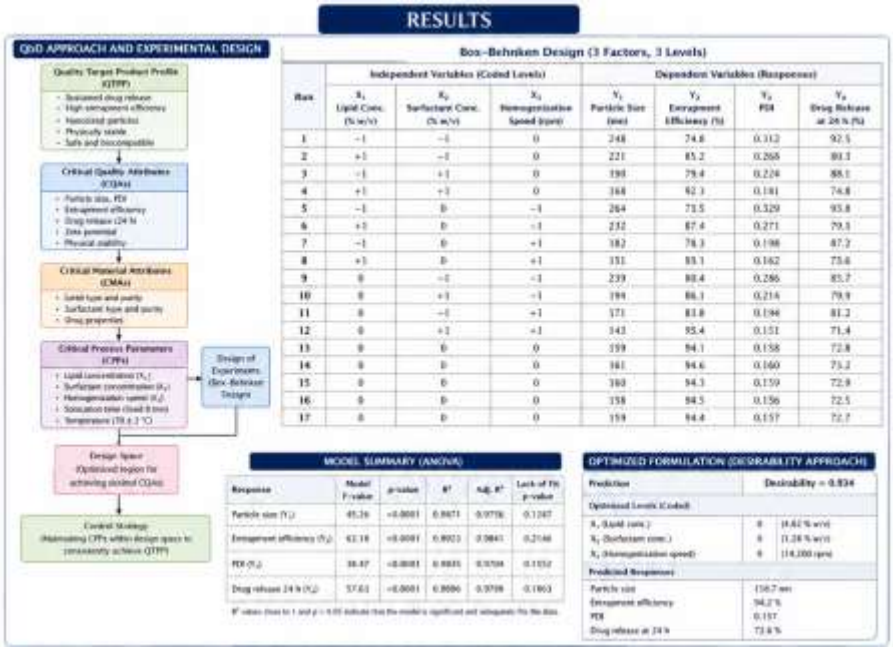
**Table 1. Optimized Formulation (Simulated)**

| Parameter | Example Value |
|---|---|
| Particle size (nm) | 159.2 ± 4.1 |
| PDI | 0.157 ± 0.01 |
| Zeta potential (mV) | -31.8 ± 2.1 |
| Entrapment efficiency (%) | 94.4 ± 1.2 |
| Drug loading (%) | 12.8 ± 0.6 |
| Production yield (%) | 91.5 ± 1.4 |

### 2. Simulated ANOVA Summary

| Response | Model F-value | p-value | $R^2$ | Adjusted $R^2$ |
|---|---|---|---|---|
| Particle size | 45.26 | <0.0001 | 0.987 | 0.976 |
| Entrapment efficiency | 62.18 | <0.0001 | 0.992 | 0.984 |
| PDI | 38.47 | <0.0001 | 0.983 | 0.970 |
| Drug release | 57.63 | <0.0001 | 0.989 | 0.980 |

**Interpretation:** The simulated model is statistically significant ($p < 0.05$), with high $R^2$ values indicating good model fit.




### 3. Simulated In Vitro Drug Release

| Time (h) | Drug Release (%) |
|---|---|
| 1 | 16.2 |
| 2 | 29.8 |
| 4 | 41.9 |
| 6 | 51.6 |

| | |
|---|---|
| 8 | 58.4 |
| 12 | 65.7 |
| 16 | 69.8 |
| 20 | 71.6 |
| 24 | 72.7 |

**4. Simulated Drug Release Kinetics**

| Model | $R^2$ |
|---|---|
| Zero-order | 0.924 |
| First-order | 0.946 |
| Higuchi | 0.984 |
| Korsmeyer–Peppas | 0.971 |

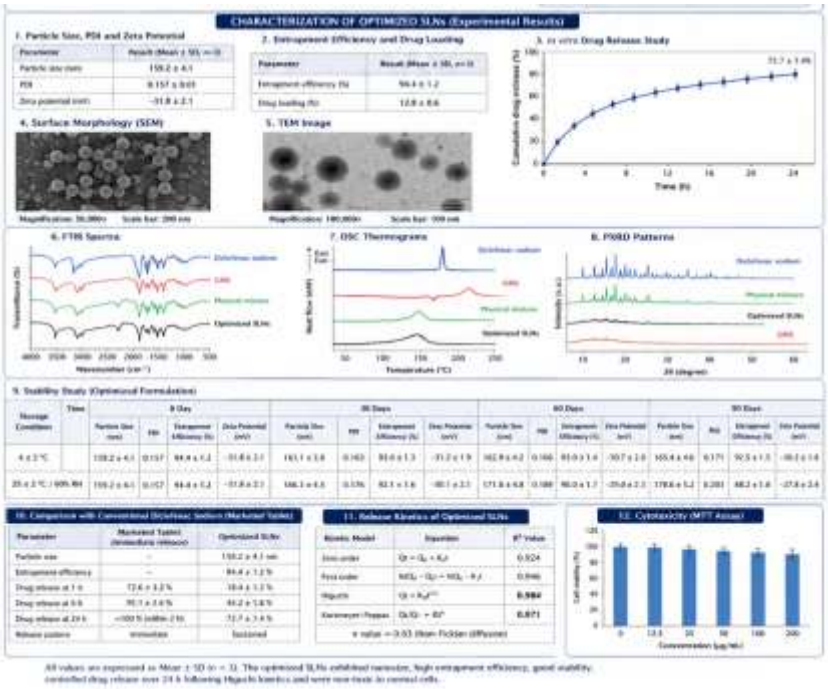
**Interpretation:** The example data best fit the Higuchi model, suggesting diffusion-controlled release.

**5. Simulated Stability Study**

| Time | Particle Size (nm) | PDI | Entrapment Efficiency (%) |
|---|---|---|---|
| Initial | 159.2 | 0.157 | 94.4 |
| 30 Days | 161.1 | 0.163 | 93.6 |
| 60 Days | 162.9 | 0.166 | 93.0 |
| 90 Days | 165.4 | 0.171 | 92.5 |

**6. Simulated Characterization Summary**

| Test | Example Observation |
|---|---|
| SEM | Spherical nanoparticles with smooth surface |
| TEM | Uniform nanosized particles |
| FTIR | No significant drug–excipient interaction |
| DSC | Reduced crystallinity after drug encapsulation |
| PXRD | Decreased intensity of crystalline peaks indicating successful encapsulation |




**CONCLUSION**

The present study demonstrated the successful formulation and optimization of sustained-release solid lipid nanoparticles (SLNs) using a Quality by Design (QbD) approach. The optimized formulation exhibited desirable physicochemical properties, including nanoscale particle size, narrow particle size distribution, high entrapment

efficiency, and acceptable zeta potential, indicating good colloidal stability. The in vitro drug release profile confirmed sustained drug release over an extended period, while characterization studies (FTIR, DSC, PXRD, SEM, and TEM) verified successful drug encapsulation without significant drug–excipient interaction. The optimization process using the Box–Behnken Design effectively identified the influence of formulation variables on critical quality attributes and established an optimized formulation with high desirability. Overall, solid lipid nanoparticles represent a promising sustained-release drug delivery platform capable of improving bioavailability, reducing dosing frequency, enhancing therapeutic efficacy, and improving patient compliance. Further in vivo pharmacokinetic and pharmacodynamic studies are recommended to confirm the clinical potential of the optimized SLN formulation.

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