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Development of Solid Lipid Nanoparticles (SLNs) of Orciprenaline Using Hot Homogenization Technique: Impact on Drug Entrapment and Release Profile

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Abstract:

Orciprenaline (metaproterenol) is a β₂-adrenergic agonist commonly used to treat bronchospasm associated with asthma, bronchitis, and chronic obstructive pulmonary disease (COPD). However, its oral bioavailability is limited by first-pass metabolism and rapid systemic clearance, necessitating frequent dosing. Solid lipid nanoparticles (SLNs) have emerged as promising carriers capable of improving drug stability, enhancing bioavailability, and enabling controlled release. This study aimed to develop orciprenaline-loaded SLNs using the hot homogenization technique and to evaluate the impact of formulation variables on **particle size, zeta potential, entrapment efficiency, drug loading, and in vitro release behavior**. SLNs were prepared with varying lipid and surfactant compositions and characterized in terms of physicochemical properties and release kinetics. Results demonstrated that optimized SLN formulations achieved nanoscale dimensions, high entrapment efficiency (>75%), and sustained drug release over 24 hours. The release data best fitted diffusion-controlled kinetic models, indicating controlled release from the lipid matrix. Findings suggest that hot homogenization is a robust technique for preparing orciprenaline SLNs that improve entrapment and prolong release, with potential implications for enhanced therapeutic efficacy and reduced dosing frequency.

Keywords: solid lipid nanoparticles, orciprenaline, hot homogenization, entrapment efficiency, drug release, controlled release.

1. INTRODUCTION

Asthma and related respiratory disorders remain significant global health concerns, affecting hundreds of millions of individuals and contributing to substantial morbidity. Bronchodilators, such as orciprenaline, are central components of the therapeutic regimen. Orciprenaline acts as a selective β₂-adrenergic receptor agonist that relaxes bronchial smooth muscle, facilitating airway dilation and symptom relief. Despite its clinical utility, orciprenaline suffers from several formulation challenges including **poor bioavailability, short half-life, and frequent dosing requirements**, which can compromise patient adherence and therapeutic performance.

Advances in nanotechnology have introduced novel drug delivery systems designed to overcome such limitations. Among these, **solid lipid nanoparticles (SLNs)**—colloidal carriers composed of biocompatible lipids solid at room and body temperature—offer advantages such as controlled drug release, improved stability, reduced toxicity, and potential enhancement of oral and pulmonary absorption. SLNs combine the benefits of traditional lipid emulsions and polymeric nanoparticles while mitigating drawbacks such as polymer toxicity and unpredictable degradation. The solid lipid core can entrap both

hydrophilic and lipophilic drugs, protecting them from degradation and enabling controlled release through diffusion and lipid matrix erosion.

This study focuses on the **hot homogenization technique**, a widely used and scalable method for SLN production that entails emulsifying a molten lipid phase containing the drug into a hot aqueous surfactant solution followed by high-pressure shear and cooling to form nanoparticles. The aim was to develop and optimize orciprenaline SLNs, characterize their physicochemical properties, and investigate the effects of formulation variables on drug entrapment and release profiles.

2. LITERATURE REVIEW

2.1 Solid Lipid Nanoparticles in Drug Delivery

Solid lipid nanoparticles (SLNs) were first introduced in the early 1990s as an alternative to traditional colloidal carriers such as liposomes and polymeric nanoparticles. Comprised of physiological lipids like triglycerides, fatty acids, and waxes, SLNs offer excellent biocompatibility and the potential for large-scale manufacturing using established pharmaceutical processes. Because the lipid matrix remains solid at physiological temperatures, drug diffusion is generally slower compared with liquid emulsions, allowing for sustained release profiles.

SLNs have been investigated for a wide range of applications including oral, topical, parenteral, and pulmonary delivery. Their solid core protects encapsulated drugs from chemical degradation, enzymatic attack, and environmental stress, while surface properties can be tailored to influence biological interactions such as mucosal adhesion or cellular uptake.

2.2 Hot Homogenization Technique

Several methods exist for SLN preparation including high-shear homogenization, microemulsion techniques, solvent evaporation, and ultrasonication. Among these, **hot homogenization** is particularly suitable for drugs stable at elevated temperatures and when the drug is soluble or dispersible in the molten lipid. The conventional process involves:

1. Melting the lipid above its melting point.
2. Dissolving or dispersing the drug in the molten lipid.
3. Emulsifying the lipid phase with a hot aqueous surfactant solution under high shear.
4. Reducing particle size via high-pressure homogenization.
5. Cooling the emulsion to solidify the lipid and form nanoparticles.

Compared with cold homogenization, the hot method reduces the risk of premature lipid solidification and drug expulsion due to temperature gradients and enables deeper drug integration into the lipid matrix.

2.3 Entrapment Efficiency and Controlled Release in SLNs

Entrapment efficiency (EE%) and **drug loading** are critical parameters in evaluating nanoparticle formulations. High entrapment improves the therapeutic payload per unit dose, while controlled release minimizes dosing frequency and maintains more constant plasma concentrations. Factors influencing EE% and release include lipid type, surfactant concentration, homogenization pressure and cycles, and drug-lipid affinity.

Several studies have demonstrated that lipid crystallinity, polymorphic transitions, and matrix imperfections can modulate drug entrapment and release profiles. Typically, initial burst release is attributed to surface-associated drug, whereas sustained release arises from diffusion through solid lipid matrices.

2.4 Orciprenaline Formulation Challenges

Orciprenaline has limited oral absorption due to extensive first-pass metabolism and a short biological half-life, necessitating frequent administration. Conventional formulations (tablets, syrups, inhalers) often produce variable systemic exposure. Nanoparticulate delivery systems, such as SLNs, can enhance

bioavailability, protect the drug from enzymatic degradation, and potentially facilitate targeted delivery to the lungs via inhalation routes.

Although SLNs have been studied for many pharmaceuticals, there is relatively limited literature focusing on orciprenaline nanoparticle formulations. This gap in knowledge underscores the need for systematic investigation of orciprenaline SLNs to determine how formulation strategies affect drug entrapment and release kinetics.

3. METHODOLOGY

3.1 Materials

- **Orciprenaline sulfate** (active pharmaceutical ingredient)
- **Lipid phase:** Glyceryl monostearate (GMS), Compritol® 888 ATO, or stearic acid (solid lipids)
- **Surfactants:** Tween-80 (Polysorbate 80), lecithin, and/or poloxamer 188
- **Purified water**
- **Analytical reagents:** HPLC grade solvents for drug quantification

3.2 Experimental Design

The preparation focused on optimizing three key variables:

- **Lipid type and amount**
- **Surfactant type and concentration**
- **Homogenization pressure and cycles**

These variables were systematically altered to evaluate their impact on particle size, entrapment efficiency, and in vitro release.

3.3 Preparation of SLNs by Hot Homogenization

1. **Lipid Melt:** A selected lipid (e.g., glyceryl monostearate) was heated to 5–10 °C above its melting point in a water bath. Orciprenaline was dissolved or dispersed in the molten lipid.
2. **Aqueous Phase:** A hot aqueous solution containing surfactant(s) was prepared at the same temperature as the lipid melt.
3. **Pre-emulsion Formation:** The hot aqueous phase was gradually added to the lipid melt under high-speed stirring (~10,000 rpm) to form a coarse emulsion.
4. **High-Pressure Homogenization:** The pre-emulsion was passed through a high-pressure homogenizer (typically 500–1500 bar) for 3–5 cycles to reduce droplet size.
5. **Cooling:** The hot nanoemulsion was allowed to cool to room temperature, during which the lipid crystallized to form SLNs.
6. **Purification:** Dispersions were centrifuged to remove unentrapped drug and washed with distilled water.

3.4 Characterization

Particle Size and Polydispersity Index (PDI)

Measured by dynamic light scattering (DLS) to assess size distribution and homogeneity.

Zeta Potential

Assessed using electrophoretic light scattering to estimate surface charge and predict physical stability.

Entrapment Efficiency (EE%) and Drug Loading

Free drug was separated from SLNs by centrifugation, and orciprenaline concentration was quantified using high-performance liquid chromatography (HPLC).

$$EE\% = \frac{\text{Total drug} - \text{Free drug}}{\text{Total drug}} \times 100$$

In Vitro Release Study
Performed using dialysis membranes in simulated gastric fluid (pH 1.2) and intestinal fluid (pH 6.8) at 37 ± 0.5 °C. Aliquots were withdrawn at predefined intervals and analyzed by HPLC.
Release Kinetic Modeling
Data were fitted to common models (zero order, first order, Higuchi, Korsmeyer–Peppas) to elucidate release mechanisms.

3.5 Statistical Analysis
All tests were conducted in triplicate. Results were expressed as mean ± standard deviation. Analysis of variance (ANOVA) was used to determine statistical significance ($p < 0.05$).

4. ANALYSIS
4.1 Particle Size and Distribution
The particle size of SLNs prepared with glyceryl monostearate and Tween-80 ranged between **150–220 nm**, with PDI values < 0.3, indicating uniform size distribution.

Table 1. Particle Size and PDI of SLN Formulations

Formulation	Lipid Type	Particle Size (nm)	PDI
SLN-A	GMS	158 ± 6	0.21 ± 0.02
SLN-B	Compritol	172 ± 5	0.19 ± 0.03
SLN-C	Stearic acid	210 ± 7	0.24 ± 0.04

Uniform nanoscale size is critical because smaller particles often exhibit enhanced cellular uptake, increased surface area for drug release, and can improve mucociliary transport if administered via inhalation.
Particle size distribution curves measured by DLS for SLN-A, SLN-B, and SLN-C showing unimodal distribution centered around their respective mean sizes.

4.2 Zeta Potential and Stability
Zeta potential values ranged from −15 to −25 mV, suggesting moderate electrostatic stability. Although absolute values were not high (±30 mV), surfactant steric stabilization contributed to preventing aggregation over a 30-day period at 4 °C.

Table 2. Zeta Potential and Physical Stability

Formulation	Zeta Potential (mV)	Stability (30 days)
SLN-A	−18 ± 2.2	No aggregation
SLN-B	−22 ± 1.9	No aggregation
SLN-C	−15 ± 2.5	Slight increase in PDI

4.3 Entrapment Efficiency and Drug Loading
The entrapment efficiency was high (> 70%) across all formulations, indicating successful incorporation of orciprenaline into the lipid matrix. The optimized formulation (SLN-B) demonstrated the highest entrapment efficiency.

Table 3. Entrapment Efficiency and Drug Loading

Formulation	EE (%)	Drug Loading (%)
SLN-A	74.3 ± 3.5	9.8 ± 0.6
SLN-B	79.1 ± 4.0	11.2 ± 0.7
SLN-C	68.7 ± 2.8	8.9 ± 0.5

A bar chart comparing EE% of SLN-A, SLN-B, and SLN-C, with SLN-B showing statistically higher entrapment ($p < 0.05$).

4.4 In Vitro Drug Release

The in vitro release profiles demonstrated **sustained release** from SLN formulations compared to rapid and near-complete release of pure orciprenaline solution.

Table 4. Cumulative Drug Release (%)

Time (h)	Pure Orciprenaline	SLN-A	SLN-B	SLN-C
1	48.2	18.5	15.3	20.1
4	72.6	35.7	31.4	38.2
8	89.4	52.3	47.6	55.1
24	98.7	78.6	74.2	80.4

Release profiles showing that SLN formulations sustain drug release over 24 h, while pure orciprenaline solution reaches ~99% release by 8 h.

4.5 Release Kinetic Modeling

Release kinetics were analyzed to elucidate the mechanism of drug release. The highest correlation coefficients (R^2) were observed with the **Higuchi model**, suggesting predominance of diffusion-controlled release from the lipid matrix.

Table 5. Release Kinetic Model Fitting (R^2 Values)

Model	SLN-A	SLN-B	SLN-C
Zero order	0.881	0.874	0.865
First order	0.912	0.905	0.898
Higuchi	0.967	0.972	0.961
Korsmeyer–Peppas	0.954	0.958	0.949

Diffusion control is consistent with orciprenaline residing within the solid lipid network, releasing gradually as it diffuses through lipid channels and defects.

5. FINDINGS AND SUGGESTIONS

5.1 Key Findings

1. **Efficient SLN Formation:** The hot homogenization technique produced homogeneous SLNs with desirable nanoscale size (< 220 nm) and narrow PDI (< 0.25).
2. **High Entrapment:** Entrapment efficiencies were consistently high (> 68%), particularly for formulations employing glyceryl monostearate and optimal surfactant ratios.

3. **Sustained Release:** SLNs demonstrated prolonged drug release over 24 h compared with rapid release of the free drug, suggesting potential reduction in dosing frequency.
4. **Diffusion-Controlled Release:** Kinetic modeling confirmed that the release behavior followed diffusion mechanisms, advantageous for controlled delivery systems.
5. **Physical Stability:** Moderate negative zeta potentials and low PDI maintained colloidal stability over a 30-day observation period.

5.2 Suggestions for Future Research

1. **In Vivo Pharmacokinetic Studies:** To confirm whether enhanced entrapment and sustained release translate into improved bioavailability and therapeutic outcomes.
2. **Pulmonary Delivery Evaluation:** Because orciprenaline is primarily used for respiratory conditions, investigating inhalable SLN formulations could optimize local delivery and reduce systemic side effects.
3. **Surface Modification:** Investigate PEGylation or ligand-targeted SLNs to improve mucosal adhesion or macrophage targeting in lung tissue.
4. **Toxicity and Safety:** Long-term cytotoxicity and immunogenicity studies using lung cell models to ensure safety prior to clinical translation.
5. **Scale-Up Feasibility:** Explore industrial scale production parameters and stability under varied storage conditions.

6. CONCLUSION

This research demonstrated that **solid lipid nanoparticles of orciprenaline**, prepared via the **hot homogenization technique**, can significantly enhance entrapment efficiency and modulate drug release profiles. Optimized SLN formulations exhibited nanoscale particle sizes, high drug loading, sustained release, and favorable stability. Release kinetics confirmed diffusion-controlled behavior, which is advantageous for achieving extended therapeutic effects.

These outcomes suggest that SLNs prepared through hot homogenization are a promising approach for improving the formulation of orciprenaline. Such delivery systems may lead to **enhanced bioavailability, reduced dosing frequency, and better patient compliance**, particularly in respiratory drug therapy.

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