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Proniosome-Derived Niosomes as a Stable Carrier for Orciprenaline: Formulation Optimization and Stability Assessment

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Abstract:
Orciprenaline sulfate is a potent bronchodilator used in the management of bronchial asthma, but its therapeutic efficacy is often limited by a short biological half-life and extensive first-pass metabolism. The present study aims to overcome these pharmacokinetic limitations by developing and optimizing proniosome-derived niosomes as a stable carrier system for sustained drug delivery. Proniosome powders were prepared using the slurry method with maltodextrin as the carrier, employing various non-ionic surfactants (Span 60 and Tween 60) and cholesterol in different molar ratios. The resulting formulations were characterized for vesicle size, entrapment efficiency, surface morphology, *in vitro* drug release, and stability. The investigation revealed that the formulation containing Span 60 and cholesterol in a 1:1 molar ratio yielded the most favorable characteristics, exhibiting a high entrapment efficiency of $78.4 \pm 1.2\%$ and an optimal vesicle size of $3.45 \mu m$. *In vitro* release studies demonstrated a biphasic release pattern with an initial burst followed by a sustained release over a 12-hour period. Furthermore, stability assessments over 90 days confirmed that the dry proniosome powder significantly retained physical integrity and drug content compared to conventional aqueous niosomal dispersions. These findings suggest that proniosome-derived niosomes offer a promising approach to enhance the stability and bioavailability of Orciprenaline, potentially improving patient compliance by reducing dosing frequency.

Keywords: Orciprenaline, Proniosome, Niosomes, Span 60, Controlled Release, Pulmonary Delivery, Stability.

1. INTRODUCTION

Orciprenaline (Metaproterenol) is a moderately selective beta-2 adrenergic agonist widely used as a bronchodilator in the management of bronchial asthma and chronic obstructive pulmonary disease (COPD). Despite its efficacy, Orciprenaline suffers from pharmacokinetic limitations, including a relatively short biological half-life (approximately 6 hours) and extensive first-pass metabolism when administered orally. This necessitates frequent dosing, which can lead to systemic side effects such as tachycardia and tremors, thereby reducing patient compliance.

Vesicular systems, particularly **Niosomes** (non-ionic surfactant vesicles), have emerged as versatile drug carriers capable of encapsulating both hydrophilic and lipophilic drugs. However, aqueous niosomal dispersions often face stability issues such as aggregation, fusion, and leakage of the entrapped drug during storage.

To circumvent these stability issues, **Proniosomes** were introduced. These are dry, free-flowing formulations coated with surfactant and lipid which, upon hydration with hot water, form a niosomal dispersion. This "dry niosome" approach combines the physical stability of a dry powder with the

biological advantages of a vesicular system. This study aims to develop Orciprenaline-loaded proniosomes to enhance stability and provide sustained drug release.

2. REVIEW OF LITERATURE

- **Vesicular Systems in Asthma:** Previous studies by *Gupta et al. (2018)* demonstrated that liposomes could effectively deliver beta-agonists to the lung, prolonging the residence time. However, the high cost of phospholipids and stability issues limited their commercial viability, shifting focus to niosomes.
- **Niosomes vs. Proniosomes:** *Vora et al. (1998)* first elaborated on the concept of proniosomes, highlighting their superiority over conventional niosomes regarding shelf-life. Research indicates that proniosomes prevent hydrolysis and oxidation of the phospholipid/surfactant components during storage.
- **Surfactant Selection:** Studies involving *Span 60* (Sorbitan monostearate) have consistently shown higher entrapment efficiencies for hydrophilic drugs compared to Tween series surfactants. This is attributed to the higher phase transition temperature () of Span 60 (), which forms a more rigid and less leaky vesicle bilayer (*Yoshioka et al., 1994*).
- **Orciprenaline Delivery:** Limited literature exists on vesicular delivery of Orciprenaline specifically. Most existing formulations are conventional tablets or syrups. Investigating proniosome technology for this specific drug fills a critical gap in sustaining its therapeutic effect.

3. MATERIALS AND METHODS

3.1 Materials

- **Drug:** Orciprenaline Sulfate (standard grade).
- **Surfactants:** Span 60, Tween 60.
- **Stabilizer:** Cholesterol (CH).
- **Carrier:** Maltodextrin.
- **Solvents:** Ethanol and Chloroform (analytical grade).

3.2 Preparation of Proniosomes

The **Slurry Method** was employed.

1. Precise amounts of surfactant (Span 60 or Tween 60) and Cholesterol were dissolved in 10 mL of chloroform:ethanol (2:1 v/v).
2. Orciprenaline sulfate was dissolved in the solvent blend.
3. Maltodextrin powder was placed in a round-bottom flask, and the surfactant/drug solution was added to form a slurry.
4. The flask was attached to a rotary evaporator. Solvent was evaporated at under reduced pressure until a dry, free-flowing powder was obtained.

3.3 Evaluation of Proniosomes

- **Conversion to Niosomes:** Proniosome powder was hydrated with phosphate buffer (pH 7.4) and agitated to form niosomes.
- **Vesicle Size Analysis:** Determined using optical microscopy and Dynamic Light Scattering (DLS).
- **Entrapment Efficiency (EE%):** The niosomal dispersion was centrifuged at 15,000 rpm for 30 minutes. The supernatant was analyzed for unentrapped drug using UV-Spectrophotometry at 276 nm.
- **Surface Morphology:** Analyzed using Scanning Electron Microscopy (SEM).

4. RESULTS AND DISCUSSION

4.1 Optimization of Formulation Variables

We evaluated two surfactants (Span 60 and Tween 60) and varying Cholesterol ratios.

Table 1: Formulation Optimization and Characterization

Formulation Code	Surfactant	Ratio (Surf:CH)	Vesicle Size ()	Entrapment Efficiency (EE %)
F1	Span 60	1 : 0.5		
F2	Span 60	1 : 1		
F3	Span 60	2 : 1		
F4	Tween 60	1 : 1		

Findings from Optimization:

- **Effect of Surfactant:** Formulations utilizing **Span 60** (F1-F3) showed significantly higher entrapment efficiency than Tween 60 (F4). Span 60 is more lipophilic (HLB 4.7) and has a higher phase transition temperature, creating a solid-like, leak-proof bilayer at physiological temperatures.
- **Effect of Cholesterol:** Increasing cholesterol (F1 to F2) increased the entrapment efficiency. Cholesterol acts as a "cement" in the bilayer, preventing leakage. However, very high surfactant ratios (F3) led to larger vesicles which can sometimes disrupt the bilayer structure, slightly lowering EE%.
- **Selected Formulation: F2** was selected as the optimized batch due to maximal entrapment and ideal size range.

4.2 Surface Morphology

SEM analysis of the optimized proniosome powder revealed that maltodextrin particles were uniformly coated with the surfactant mixture. Upon hydration, the vesicles appeared spherical and distinct with smooth boundaries, confirming the formation of niosomes.

4.3 In Vitro Drug Release

The release study was conducted in Phosphate Buffer (pH 7.4) over 12 hours.

- **Pure Drug:** 90% release within 2 hours.
- **Formulation F2:** Showed a biphasic release pattern—an initial burst release (25% in 1 hour) followed by a sustained release (72% cumulative release at 12 hours). The burst effect is beneficial for immediate bronchodilation, while the sustained phase maintains therapeutic levels.

4.4 Stability Studies

Stability was assessed for the optimized F2 formulation (stored as dry proniosome powder) vs. hydrated liquid niosomes at and .

Table 2: Stability Assessment (Percentage Drug Retained after 90 Days)

Storage Condition	Formulation Form	Initial Drug Content (%)	After 30 Days	After 90 Days
(Refrig)	Liquid Niosomes	100		
	Dry Proniosomes	100		
(Room)	Liquid Niosomes	100		
	Dry Proniosomes	100		

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Findings from Stability: The dry proniosome powder showed superior stability compared to liquid niosomes. Liquid dispersions suffered from drug leakage (likely due to hydrolysis or fusion of vesicles) over time. The dry powder form effectively restricted the mobility of the surfactant and drug, preventing leakage.

4.5 Entrapment Efficiency (EE%) Optimization

The entrapment efficiency is a critical parameter governing the therapeutic potential of the carrier.

- **Surfactant Hydrophile-Lipophile Balance (HLB):** Formulation **F2 (Span 60)** exhibited significantly higher entrapment ($78.4 \pm 1.2\%$) compared to Tween 60 ($54.6 \pm 1.8\%$) ($p < 0.05$). This can be attributed to the lower HLB value of Span 60 (4.7) compared to Tween 60 (14.9) and the longer saturated alkyl chain of Span 60 (C_{18}), which results in a higher phase transition temperature ($T_c \approx 53^\circ C$). This creates a more rigid and less leaky bilayer at room temperature.
- **Role of Cholesterol:** The addition of cholesterol up to a 1:1 ratio (Surf:CH) significantly improved EE%. Cholesterol acts as a "vesicular cement," orienting itself in the bilayer to fill the voids between surfactant molecules, thereby increasing microviscosity and preventing drug leakage. However, increasing cholesterol beyond this ratio (2:1) disrupted the regular linear structure of the vesicular membrane, leading to a slight decrease in entrapment.
- Kinetic Data Analysis of Optimized Formulation (F2)

Kinetic Model	R2 Value	Release Exponent (n)	Interpretation	Column 1
Zero Order	0.892	-	Constant release rate	•
First Order	0.945	-	Concentration dependent	•
Higuchi	0.988	-	Diffusion controlled	•
Korsmeyer-Peppas	0.972	0.54	Non-Fickian transport	•
				•

Interpretation: The release best fitted the **Higuchi model** ($R^2 = 0.988$), indicating that the primary mechanism of drug release is diffusion through the gel-like niosomal bilayer.

5. CONCLUSION

The present study successfully demonstrates that **proniosome technology** is a viable strategy to overcome the stability limitations associated with conventional vesicular systems. The optimized formulation, utilizing **Span 60 and Cholesterol (1:1)** with maltodextrin as a carrier, achieved a high entrapment efficiency (78.4%) and a desirable particle size for potential pulmonary delivery.

The formulation exhibited a diffusion-controlled, sustained release profile over 12 hours, which supports the hypothesis that this system could reduce the dosing frequency of Orciprenaline. Most importantly, the dry proniosome powder exhibited excellent physicochemical stability over three months. Consequently, proniosome-derived niosomes represent a promising, stable, and scalable approach for the management of bronchial asthma, warranting further *in vivo* investigation.

Key conclusions include:

1. **High Entrapment:** The optimized formulation achieved nearly 78% entrapment efficiency.
2. **Sustained Release:** The system extended drug release up to 12 hours, which suggests a potential reduction in dosing frequency from 3-4 times daily to twice daily.

3. **Superior Stability:** The proniosome approach solved the critical issue of niosome instability. The dry powder retained >94% of the drug even after 3 months at room temperature.

Therefore, proniosome-derived niosomes represent a viable, stable, and effective alternative carrier system for the pulmonary or oral delivery of Orciprenaline.

6. SUGGESTIONS AND FUTURE PERSPECTIVES

Based on the findings of this study, the following suggestions are proposed for future research to translate this formulation from bench to bedside:

1. **Aerodynamic Characterization:** Since Orciprenaline is a bronchodilator, future studies should utilize an **Anderson Cascade Impactor** to determine the Mass Median Aerodynamic Diameter (MMAD). This ensures the particles are in the respirable range (1–5 μm) for deep lung deposition.
2. **Zeta Potential Analysis:** To further predict long-term stability, Zeta potential measurements should be conducted. A potential value greater than $\pm 30 mV$ would indicate high colloidal stability due to electrostatic repulsion.
3. **In Vivo Pharmacokinetics:** Animal studies (e.g., in Wistar rats or Beagle dogs) are required to correlate the *in vitro* sustained release data with *in vivo* plasma concentration profiles and to calculate the Mean Residence Time (MRT) in the lungs.
4. **Toxicity Studies:** A histopathological examination of lung tissue in animal models should be conducted to ensure that the surfactant (Span 60) and carrier (Maltodextrin) do not cause alveolar inflammation or ciliotoxicity upon chronic usage.

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