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Assessing the impact of Span 60 and cholesterol on mupirocin niosomes developed for topical delivery

Noor Yousif Fareed[1], Ghada Hamid Naji[2,*], Worood Hameed Al-Zheery[3]

[1]Department of Pharmaceutics, College of Pharmacy, University of Basrah, Basrah, Iraq
[2]Department of Pharmaceutics, College of Pharmacy, University of Babylon, Hillah, Iraq
[3]Department of Pharmaceutics, College of Pharmacy, Al-Esraa University, Baghdad, Iraq

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ABSTRACT

Mupirocin (MUP), a broad-spectrum antibacterial agent, is commonly used in order to treat superficial skin infections. However, its therapeutic efficacy is limited by poor skin permeability and the impracticality of prolonged topical administration. This study reports the development of a niosomal delivery system engineered so as to enhance topical MUP delivery by optimizing vesicle size and drug entrapment efficiency. Niosomes were prepared using the thin-film hydration method, and a 2^2 full factorial design was employed in order to optimize formulations based on Span 60 and cholesterol concentrations. Vesicle size and entrapment efficiency served as dependent variables. Both models were significant, thereby indicating that formulation variables and their interactions substantially influenced vesicle characteristics. The findings demonstrate that a full factorial design is an effective approach to elucidate and optimize the impact of formulation variables on MUP-loaded niosomes.

1. Introduction

The broad-spectrum antimicrobial activity and antibiofilm properties of mupirocin (MUP) make it a widely used treatment for superficial topical infections. MUP inhibits its bacterial protein synthesis by reversibly blocking isoleucyl-tRNA synthetase. Its distinctive mechanism of action may explain its lack of cross-resistance with other antibiotics[1]. Crystalline MUP has a molecular weight of 500.6 g/mol and appears white to off-white. Its maximum aqueous solubility is

*** CORRESPONDING AUTHOR:**
Ghada Hamid Naji, Department of Pharmaceutics, College of Pharmacy, University of Babylon, Hillah, Iraq; e-mail: phar.ghadah.hamid@uobabylon.edu.iq

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0.0265 g/L. Exhibiting lipid-soluble behavior, it has a partition coefficient (Log P) of 2.45. Clinically, MUP is used for topical skin infections and nasal decolonization of *Staphylococcus aureus*. However, its limited skin permeability and the absence of sustained drug release hamper its topical effectiveness[2].

Niosomes are vesicular carriers composed of non-ionic surfactants and cholesterol, which enhance membrane stability[3]. These carriers primarily localize within the stratum corneum, increasing drug residence time and enhancing skin permeation while minimizing systemic absorption. Studies suggest that niosomes improve intercellular lipid fluidity and reduce the barrier function of the epidermis, thereby increasing drug permeability[4]. This study aimed at formulating MUP-loaded niosomes for topical delivery, using a 2^2 full-factorial experimental design in order to optimize vesicle size and entrapment efficiency (EE%).

2. Methodology

2.1. Materials

MUP was sourced from Hangzhou Hyper Chemicals Limited (China). Span 60 and cholesterol were procured from Xi'an Sonwu Biotech Co., Limited (China). Methanol and chloroform were supplied by Alpha Chemicals.

2.2. Experimental design

The effects of Span 60 and cholesterol concentrations on MUP niosomal EE% and particle size (PS) were examined using a 2^2 full-factorial design comprising 4 base runs and 8 total runs, performed in duplicate (see Table 1). The experimental framework was developed using the Design Expert software. Blocking was implemented in order to minimize confounding variables, enhance precision, and address operational constraints. Data analysis was conducted with the Design Expert software (version 13), employing analysis of variance (ANOVA) in order to compare formula means. Statistical significance was set at $p<0.05$.

2.3. Preparation of MUP niosomes

Niosomal formulations of MUP were prepared by the thin-film hydration method. Table 1 outlines the formulation components. In brief, MUP, Span 60, and cholesterol were dissolved in 15 mL of a methanol–chloroform mixture (2:1, v/v). The solution was transferred to a 250-mL round-bottom flask equipped with a rotary evaporator (IKA RV8, USA). Solvent evaporation under reduced pressure at 60°C and 100 rpm over 30 min yielded a translucent thin film on the flask walls. Subsequently, 10 mL of distilled water were added in order to hydrate the film, followed by rotation at 150 rpm in a 70°C water bath for 1 h. The resulting dispersion was sonicated in a bath sonicator for 30 min in order to reduce PS, then refrigerated overnight at 4°C so as to stabilize the vesicular membranes.

2.4. Characterization of MUP niosomes

Vesicle size was measured by dynamic light scattering using the Zetasizer Nano ZS (Malvern Instruments, UK). For optimal scattering intensity, the niosomal dispersion was diluted (1:10) in distilled water5. Ultrafiltration was employed in order to determine the EE%, based on the quantification of unencapsulated MUP in the supernatant, measured spectrophotometrically at 226 nm. The EE% was calculated by using the following formula5:

EE% = [(total amount of drug added – free drug) / (total amount of drug added)] × 100%

3. Results and Discussion

Characterization data are presented in Table 1. The full-factorial ANOVA has revealed that the particle size model was statistically significant ($p<0.0001$), thereby indicating that the component concentrations and their interactions substantially influenced PS. Span 60 exerted a significant main effect ($p<0.0001$), while cholesterol did not ($p=0.2319$); however, their interaction was found to be highly significant ($p=0.0012$).

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Table 1. Preparation and characterization parameters for the herein assessed mupirocin (MUP) niosomes. Abbreviations used: EE%, entrapment efficiency; PS, particle size.

Run order	**Blocks**	**MUP** (mg)	**Span 60** (mg)	**Cholesterol** (mg)	**PS** (nm)	**EE%**
1	1	5	86	67.6	180	30%
2	1	5	86	33.8	130	50%
3	1	5	172	67.6	210	67%
4	1	5	172	33.8	260	75%
5	2	5	172	67.6	213	68%
6	2	5	86	67.6	185	32%
7	2	5	172	33.8	255	75%
8	2	5	86	33.8	130	50%

require optimization of PS, as smaller vesicles penetrate skin layers more efficiently[6]. Increasing surfactant concentration markedly enlarged the vesicle size, likely due to the long alkyl chain of Span 60 facilitating large vesicle formation[7].

ANOVA has also indicated a significant model for EE% (p<0.0001), thereby confirming that the component concentrations and their interaction influence drug encapsulation. Both Span 60 (p<0.0001) and cholesterol (p<0.0001) had significant individual effects, and their interaction was also significant (p=0.0012).

High drug loading is critical for effective topical delivery. MUP, a lipophilic compound with a Log P of 2.45, preferentially partitions into the lipid bilayers of niosomes[8]. Span 60 was selected due to its advantageous physicochemical characteristics, being a solid state at ambient temperature (melting point, T_m: 53°C), long alkyl chain, and high lipophilicity (low hydrophilic–lipophilic balance), which promote stable vesicle formation and high MUP entrapment[9].

Balancing cholesterol and non-ionic surfactant concentrations is essential for maximizing the EE%. Insufficient cholesterol may cause drug leakage and vesicle fusion, while excess surfactant can enhance the lipophilic environment, thereby improving drug entrapment. Conversely, low surfactant levels produce fewer vesicles, which limit drug loading capacity[10].

4. Conclusion

The findings of this study support the use of vesicular carriers in order to enhance topical delivery of MUP and improve clinical efficacy. Niosomes prepared *via* thin-film hydration, using Span 60 as a surface-active agent and cholesterol as a membrane stabilizer, have herein demonstrated promising attributes for dermal drug delivery.

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Conflicts of interest

None exist.

ORCIDs

0000-0003-2570-607X (N.Y. Fareed); 0000-0002-5208-546X (G.H. Naji); 0000-0001-7531-6948 (W.H. Al-Zheery)

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