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Development of Cefoperazone Loaded Glycerosomes: Fabrication, Optimization, and *in vitro* evaluation of the antimicrobial and wound healing activities

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KEYWORDS

Cefoperazone, Glycerosomes, Nanoparticles, Antibiotic, scratch wound healing, agar diffusion, MIC

SHORT SUMMARY

Cefoperazone is a broad-spectrum cephalosporin antibiotic used for the treatment of bacterial infections in various locations, including the respiratory tract and abdomen. However, bacterial resistance restricted its applications. The aim of the present study was to improve the efficacy of Cefoperazone and decrease its bacterial resistance through nano-encapsulation of Cefoperazone into glycerosomes vesicles. Optimization of Cefoperazone loaded glycerosomes was achieved using Design expert 3^2 full factorial design. Three independent variables were used namely cholesterol amount (mg), lecithin amount (mg) and glycerol concentration (%) while particle size, PDI, zeta potential and entrapment were the measured responses. The optimized formula was further evaluated for its anti-microbial activity as well as wound healing effect. The Cefoperazone loaded glycerosomes were successfully prepared and optimized. Anti-microbial study of optimized Cefoperazone loaded glycerosomes using agar diffusion method effectively inhibited bacterial growth in all tested strains. Minimum inhibitory concentration (MIC) of Cefoperazone loaded glycerosomes showed enhanced antimicrobial activity compared to free Cefoperazone with 2, 4 and 8 folds against staphylococcus aureus, pseudomonas aeruginosa and escherichia coli, respectively. Scratch wound assay showed enhanced wound healing activity of the Cefoperazone loaded glycerosomes optimized formula compared to free Cefoperazone. Consequently, the developed formulations showed prosperous potentials for the enhanced delivery of Cefoperazone.

EXTENDED ABSTRACT

Cefoperazone (a third generation Broad-spectrum cephalosporin) is used for Endometritis, Peritonitis, Respiratory tract infection, Pelvic Inflammatory disease, Skin infection, Septicemia and wound healing [1]. However, Cefoperazone suffered from many challenges including drug resistance caused by ß-lactamases and chromosomal enzymes produced by bacteria, Plasmid-mediated ß-lactamases (PMBLs) [2].

The aim of the current study was to load Cefoperazone into glycerosomes to overcome its limitations and enhance its therapeutic activity.

Preparation of Cefoperazone loaded Glycerosomes

Glycerosomes were prepared using thin film hydration method [3]. Lecithin, tween 80 and cholesterol were dissolved in DCM to form the organic phase. Then, organic phase was evaporated using rotary evaporator to form a thin film. Afterwards, the thin film was rehydrated using solution of drug and glycerol in deionized water and were further rotated using rotary evaporator for 1 hour at 45 ^{O}C and 60 rpm. Lastly, the formed dispersion was sonicated using probe sonicator for 5 min at 70% amplitude.

Construction of the experimental design

Design expert 3^2 full factorial design was utilized to optimize Cefoperazone loaded glycerosomes using three different independent variables (cholesterol amount (mg), lecithin amount (mg) and glycerol concentration (%)) at two levels with minimum number of runs then the dependent responses including particle size, polydispersity

index (PDI), zeta potential and entrapment efficiency were measured.

Characterization of optimized Cefoperazone loaded Glycerosomes

Optimized Cefoperazone loaded glycerosomes was characterized for particle size, PDI, zeta potential, entrapment, morphology using transmission electron microscope and *in vitro* drug release using cellulose dialysis bags.

Results

The eight obtained formulae were successfully prepared and characterized. the influences of independent variables on the measured responses are illustrated in Figure 1.

The optimized Cefoperazone loaded glycerosomes showed spherical shaped nanoparticles as demonstrated in Figure 2. Furthermore, cumulative drug release demonstrated a biphasic release pattern with burst release followed by sustained release as shown in Figure 3. Anti-microbial study of optimized Cefoperazone loaded glycerosomes using agar diffusion method successfully inhibited bacterial growth in all tested strains as illustrated in Figure 4. Minimum inhibitory concentration (MIC) of Cefoperazone loaded glycerosomes showed enhanced antimicrobial activity compared to free Cefoperazone with 2, 4, and 8 folds for staphylococcus aureus, pseudomonas aeruginosa and escherichia coli, respectively. Scratch wound assay showed enhanced wound healing activity of optimized Cefoperazone loaded glycerosomes compared to free Cefoperazone (Figure 5).

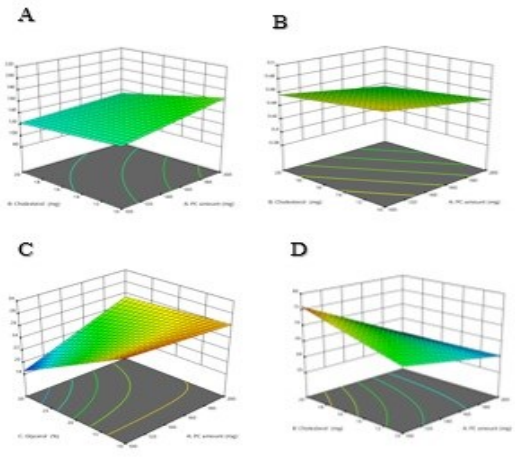

Figure 1 3D response surfaces, A: Particle size, B: PDI, C: Zeta Potential, D:Entrapment efficiency

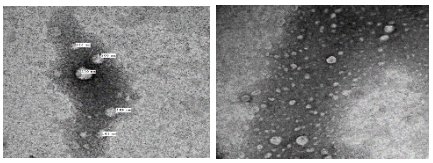

Figure 2 Transmission electron microscope of optimized formula

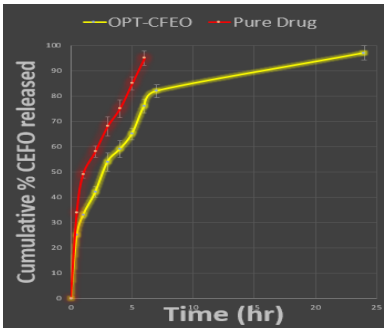

Figure 3 Cumulative drug released from optimized Cefoperazone loaded glycerosomes and free Cefoperazone

Figure 4 Agar diffusion test for A: pseudomonas aeruginosa B: escherichia coli C: staphylococcus aureus

Figure 5 Results of scratch wound assay

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