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Original Article

One-step lipid–polymeric hybrid nanoparticles as intracanal drug delivery system: Synthesis, characterization, antimicrobial activity, and dentinal penetration

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Highlights

- CIP-LPNPs & CS-LNPs boost drug performance vs. free drugs.
- NPs sized ~140 nm & ~131 nm with stable zeta potentials.

- CS-LNPs give 2× lower MICs & deeper dentinal penetration.
- Both nanoformulations enhance biofilm eradication against pathogens.
- Hybrid lipid-polymer gels improve physicochemical & antibiofilm traits.

Abstract

Introduction

This study developed two lipid–polymeric hybrid nanoparticle thermosensitive gels, hypothesizing enhanced physicochemical properties, antimicrobial efficacy, and dentinal penetration compared to free drugs.

Methods

Ciprofloxacin-loaded lecithin–PLGA nanoparticles (CIP-LPNPs) and chitosan–lecithin nanoparticles (CS-LNPs) were synthesized via nanoprecipitation and characterized by DLS, SEM, FTIR and HPLC. Antimicrobial activity against *Enterococcus faecalis*, *Escherichia coli* and *Pseudomonas aeruginosa* was assessed by disk diffusion, MIC and biofilm assays; dentinal penetration of FITC-labeled CS-LNPs was evaluated by confocal microscopy.

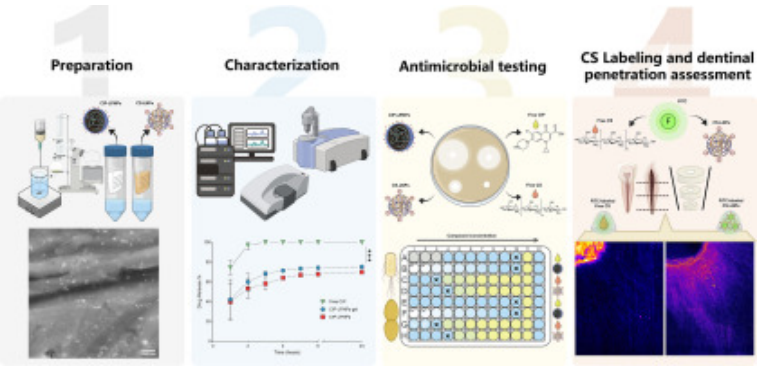
Results

CIP-LPNPs and CS-LNPs measured 140.6 and 130.9 nm with zeta potentials of −29.4 and +28.9 mV, respectively. CIP-LPNPs showed 55.7% encapsulation and biphasic release. Both nanoparticles enhanced biofilm eradication against all strains; CS-LNPs exhibited two-fold lower MICs and significantly deeper tubular penetration than free chitosan ($p < 0.0001$).

Conclusions

Both CIP-LPNPs and CS-LNPs improved physicochemical and antibiofilm properties over their free drugs; however, as no biocompatibility assessment was performed, these formulations cannot be considered safe without such validation.

Graphical abstract



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Introduction

Persistent root canal infections continue to represent one of the most challenging problems in endodontic practice, carrying a substantial clinical and global health burden.[1] Despite significant advances in instrumentation and chemical disinfection methods, complete microbial eradication is rarely achieved. This limitation is primarily attributed to two interrelated factors: the polymicrobial nature of endodontic infections, which comprise more than 500 identified microbial species[2]; and the intricate, highly variable morphology of the root canal system. Anatomical complexities such as isthmuses, lateral canals, and dentinal tubules create isolated niches where microorganisms can persist, remaining inaccessible to host immune responses and vascular supply.3, 4 Moreover, bacterial penetration into dentinal tubules has been documented to extend up to 1500μm,[5] exceeding the reach of conventional irrigants and intracanal medicaments.6, 7 Consequently, the antimicrobial efficacy of current disinfection strategies remains limited.

Current treatment strategies rely on mechanical instrumentation combined with chemical irrigation, often supplemented by intracanal medicaments to reduce residual microbial load between visits.[8] Among these, calcium hydroxide remains the most widely used due to its strong alkalinity and broad-spectrum antimicrobial properties.[9] Antibiotic-based formulations have also been explored, such as ciprofloxacin–metronidazole combinations, in which ciprofloxacin effectively targets Gram-negative facultative bacteria while metronidazole acts against obligate anaerobes.[10] More recently, natural polymers such as chitosan have been investigated for intracanal delivery due to their intrinsic antibacterial effects, biocompatibility, and ability to adhere to dentin surfaces. Despite these efforts, microbial persistence remains a frequent outcome,[11] particularly with resistant species such as *Enterococcus faecalis*, a facultative anaerobic species implicated in 32–70% of refractory cases, reaching up to 90% in some reports.12, 13, 14, 15, 16 This pathogen is particularly problematic due to raised concerns about its resistance to calcium hydroxide and ability to contribute to biofilm stability rather than disrupt it17, 18 Furthermore, reliance on antibiotic pastes raises concerns about the development of bacterial resistance against the very drugs used in treatment.[19]

To overcome these limitations, research has shifted toward nanotechnology-based intracanal disinfection systems The growing interest in nanoparticle-based therapeutic platforms across

biomedical applications, including targeted drug delivery, bioimaging, biosensing, and controlled therapeutic release, reflects their capacity for surface functionalization and tunable physicochemical properties.[20]Nanoparticles possess unique physicochemical properties such as small size, surface charge, shape, and tunable drug-release profiles that enable them to penetrate biofilms, disrupt bacterial membranes, and reduce the emergence of resistant strains.21, 22 Several nanoparticle systems have been studied, including non-biodegradable metallic nanoparticles (e.g., silver, zinc)[23] and biodegradable polymeric carriers (e.g., PLGA-based formulations).24, 25

Among these, lipid–polymeric hybrid nanoparticles (LPHNPs) represent a particularly promising platform. By combining the high loading capacity and biocompatibility of lipid carriers with the structural stability and sustained-release capability of polymeric systems, LPHNPs offer a dual advantage ideal for intracanal environments,[26] Complementary to this system, thermosensitive hydrogels such as Poloxamer 407 and 188 exhibit injectable fluidity at room temperature and undergo gelation at body temperature, serve as vehicles providing controlled antimicrobial release.27, 28, 29

For the present study, ciprofloxacin was selected as the model antibiotic given its activity against *E. faecalis* and other relevant endodontic pathogens,16, 30, 31, 32 In parallel, chitosan, a biocompatible cationic polysaccharide, was investigated as a non-antibiotic, intrinsically antibacterial option owing to its biodegradability and natural bioactivity.[33] To the best of our knowledge, this investigation is the first to evaluate chitosan–lecithin nanoparticles (CS-LNPs) as a non-antibiotic, self-active antimicrobial platform with penetration into dentinal tubules, and develop a lecithin–PLGA-based hybrid nanoparticle system loaded with ciprofloxacin (CIP-LPNPs), incorporated into a thermosensitive gel, for direct comparison to their free drug counterparts.

Section snippets

Chemicals and reagents

Ciprofloxacin (batch #2401001R) was procured from JK Chemicals, India. Low molecular weight chitosan (batch #STBF8219V), Poly(D,L-lactide-co-glycolide) Resomer® RG 503H 50:50 (Mw 24,000–38,000), acetic acid, dialysis sacks with a molecular weight cut-off of 12,000Da (batch #SLBQ4638V), and oleic acid were obtained from Sigma-Aldrich, Germany. Lecithin (containing 51.9% phosphatidylcholine and 12.5% phosphatidylethanolamine, batch #20617HHFEA) was supplied by Cargill, Germany. Acetone and …

Ciprofloxacin concentration-response relationship

HPLC analysis of ciprofloxacin produced distinct and symmetrical peaks with a retention time of 3.2 min. The calibration curves demonstrated excellent linearity over a concentration range of 0.97–500 μg/ml, with correlation coefficients (R^2) reaching 0.996, indicating a strong fit. The variation between the actual and measured concentrations was consistently within 2%, reflecting a high degree of accuracy and a narrow margin of error at a 95% confidence level. Furthermore, the random …

Discussion

CIP-LPNPs and CS-LNPs were successfully synthesized using a one-step nanoprecipitation method with uniform size and high encapsulation efficiency. In the CIP-LPNPs formulation, ciprofloxacin solubilized in oleic acid was encapsulated within a poly(lactic-co-glycolic acid) (PLGA) matrix via a co-nanoprecipitation mechanism. PLGA polymer provides a biodegradable and biocompatible structure that facilitates sustained drug release.37, 38 Lecithin, as the phospholipid with its surfactant behavior …

Abbreviations

CIP-LPNPs	Ciprofloxacin-loaded lecithin-PLGA nanoparticles
CS-LNPs	Chitosan–lecithin nanoparticles
CLSM	Confocal laser scanning microscopy
EE%	Encapsulation efficiency
FITC	fluorescein isothiocyanate
NaOCl	Sodium hypochlorite
EDTA	Ethylenediaminetetraacetic acid
GRAS	Generally recognized as safe
ZOI	Zone of inhibition
MPD	Mean penetration depth
PDI	Polydispersity index
DLS	Dynamic light scattering
SEM	Scanning Electron Microscopy
FTIR	Fourier-transform infrared spectroscopy
HPLC	High-performance liquid chromatography
MIC	

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CRediT authorship contribution statement

Ahmad AlMukhallalati: Writing – original draft, Visualization, Validation, Investigation, Formal analysis, Data curation, Methodology. **Amal Yousfan:** Writing – original draft, Validation, Methodology, Formal analysis. **Diego Hidalgo-Martínez:** Software, Methodology, Formal analysis. **Samer Ibrahim:** Validation, Supervision. **Khitam Al Moarrawi:** Validation, Supervision. **Abdulsamie Hanano:** Writing – review & editing, Supervision, Methodology, Conceptualization. …

Declaration of competing interest

The authors declare that there is no conflict of interest. …

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