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A Study on the Formulation and Optimization of Nanostructured Lipid Carriers for Bempedoic Acid with Improved Biorelevant Intestinal Solubilization

S. Venkat Naveen[1*], I. Nagaraju[1], G. S. Valluri[1], G. Vijaya Kumar[2]

[1]Department of Pharmaceutics, KGR Institute of Technology and Management, Rampally, Rangareddy, Telangana, India
[2]KGR Institute of Technology and Management, Rampally, Rangareddy, Telangana, India

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Abstract

Bempedoic acid is an ATP-citrate lyase inhibitor used to reduce low-density lipoprotein cholesterol; however, its poor aqueous solubility under acidic conditions and pH-dependent dissolution may limit gastrointestinal drug availability. This study aimed to develop and optimize an aqueous nanostructured lipid carrier (NLC) dispersion to improve bempedoic acid release and biorelevant intestinal solubilization. Pre-formulation screening evaluated drug solubility in solid and liquid lipids, lipid–aqueous partitioning, drug–excipient compatibility, and surfactant emulsification. Precirol® ATO 5 and Capryol® 90 were selected as the solid and liquid lipid components, respectively, at an 80:20 ratio; Tween® 80 and Poloxamer 188 were selected as the stabilizer system. NLCs were prepared by hot homogenization followed by probe ultrasonication. The optimized dispersion exhibited a particle size of 145.8 ± 4.9 nm, polydispersity index (PDI) of 0.21 ± 0.02, zeta potential of −24.7 ± 1.5 mV, entrapment efficiency of 86.3 ± 2.4%, drug loading of 4.6 ± 0.3%, and drug content of 98.9 ± 1.7%. In pH-shift release testing, cumulative release at 24 h was 79.3 ± 3.1% for NLCs compared with 28.7 ± 2.2% for plain drug suspension. Release data were best fitted by the Korsmeyer–Peppas model (R^2 = 0.989; n = 0.52). During pH-stat lipolysis, 67.9 ± 3.4% of the drug remained in the micellar/aqueous fraction for NLCs compared with 24.6 ± 2.8% for suspension. The dispersion maintained its quality more effectively at 4°C than at 25°C over 30 days, whereas accelerated storage produced particle growth and PDI increase. The findings demonstrate improved in vitro release and digestion-phase solubilization; in vivo pharmacokinetic confirmation remains necessary.

Keywords: Bempedoic acid; intestinal solubilization; lipid-based formulation; lipolysis; nanostructured lipid carriers

1 Introduction

Elevated low-density lipoprotein cholesterol (LDL-C) is an established modifiable risk factor for atherosclerotic cardiovascular disease. Although statins remain the principal first-line treatment, intolerance or adverse effects can limit their use in some patients, supporting the need for additional LDL-C-lowering therapies [1, 2]. Bempedoic acid is an ATP-citrate lyase inhibitor that acts upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase in cholesterol biosynthesis. Its activation is predominantly hepatic, and clinical studies have demonstrated LDL-C-lowering efficacy [3, 4].

The oral performance of poorly water-soluble drugs can be limited by dissolution and precipitation during gastrointestinal transit. Lipid-based delivery systems can improve drug dispersion and maintain a solubilized fraction during digestion through the formation of colloidal digestion products and mixed micelles [5]–[8]. Nanostructured lipid carriers are composed of a solid lipid matrix

combined with a liquid lipid and stabilized by surfactants. The liquid lipid introduces imperfections into the crystalline matrix, potentially increasing drug accommodation and reducing drug expulsion during storage [9, 10].

The present work investigated an aqueous bempedoic acid-loaded NLC dispersion using pre-formulation-guided excipient selection, screening-based optimization, physicochemical characterization, in vitro release, pH-stat lipolysis, and stability assessment. The primary objective was to determine whether the optimized NLC could improve drug release and maintain bempedoic acid in the solubilized micellar/aqueous fraction under simulated intestinal digestion. The developed product was a liquid NLC dispersion; no tablet or capsule was manufactured.

2 Materials and methods

2.1 Materials

Bempedoic acid was used as the active pharmaceutical ingredient. The screened solid lipids included glyceryl monostearate, Precirol® ATO 5, Compritol® 888 ATO, stearic acid, and cetyl palmitate. Liquid lipids included Capryol® 90, Labrafac™ PG, oleic acid, isopropyl myristate, and medium-chain triglyceride oil. Tween® 80, Poloxamer 188, and Kolliphor® RH 40 were evaluated as surfactants/stabilizers. Methanol was used for UV analysis; buffer salts, sodium taurocholate, lecithin, calcium chloride, pancreatin/pancreatic lipase, and sodium hydroxide were used in release and lipolysis experiments.

2.2 Pre-formulation and analytical studies

Solid-lipid solubility was determined by adding excess bempedoic acid to molten lipid, equilibrating under stirring, separating undissolved drug by warm centrifugation, and quantifying the recovered drug by UV spectrophotometry. Liquid-lipid solubility was evaluated by a shake-flask method at 37°C for 24 h. Partition behavior was assessed in lipid or n-octanol and phosphate buffer (pH 6.8), using a 1:1 phase ratio; the partition coefficient was calculated as the ratio of lipid-phase to aqueous-phase concentration. Drug–excipient compatibility was assessed by FTIR comparison of pure drug, excipients, and physical mixtures. Differential scanning calorimetry (DSC) was used to establish the pure-drug thermal baseline. Bempedoic acid was quantified in methanol at 258 nm using calibration standards from 0.5 to 20 μg/mL.

Surfactant systems were screened using percentage transmittance at 600 nm and visual stability for 2 h. Solid-to-liquid lipid ratios of 90:10, 80:20, and 70:30 (w/w) were compared using particle size, PDI, zeta potential, and 24 h physical stability. Triplicate results were expressed as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) was used for the reported screening comparisons.

2.3 Preparation and optimization of NLCs

Bempedoic acid was incorporated into the molten solid/liquid lipid blend. A separately prepared aqueous surfactant phase was heated to the same temperature. The lipid phase was added gradually to the aqueous phase under high-shear homogenization, followed by probe ultrasonication in pulse mode with temperature control. The dispersion was cooled under gentle stirring to recrystallize the lipid matrix and stored in airtight amber vials. The selected formulation contained Precirol® ATO 5 (2.4% w/v), Capryol® 90 (0.6% w/v), Tween® 80 (1.5% w/v), Poloxamer 188 (0.5% w/v), bempe-

doic acid (0.2% w/v), and purified water q.s. The 80:20 lipid ratio was selected through predefined screening constraints rather than a response-surface or central-composite design.

2.4 Physicochemical characterization

Particle size, PDI, and zeta potential were measured by dynamic light scattering/electrophoretic mobility analysis after suitable dilution. Entrapment efficiency was determined after separation and quantification of free drug. Drug content was measured after disrupting the NLC dispersion in methanol. Entrapment efficiency was calculated as [(total drug − free drug)/total drug] × 100; drug loading was calculated as [entrapped drug/(lipid + drug)] × 100. FTIR and powder X-ray diffraction (XRD) were used to compare pure bempedoic acid, blank NLC, and drug-loaded NLC. Particle morphology was examined by transmission and scanning electron microscopy (TEM and SEM); DLS remained the quantitative particle-size method.

2.5 In vitro release, lipolysis, and stability

Drug release from the optimized NLC and plain bempedoic acid suspension was compared by dialysis-bag diffusion at 37 ± 0.5°C under agitation. The medium underwent a pH shift from pH 1.2 to pH 6.8. Samples were collected through 24 h and quantified at 258 nm. Release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. Biorelevant digestion was evaluated by pH-stat lipolysis at 37°C using bile salt, lecithin, calcium, buffer, and pancreatin/pancreatic lipase; pH was maintained near 6.5 by NaOH titration. After digestion and phase separation, drug in the micellar/aqueous and pellet/precipitate fractions was quantified. Stability was assessed at 4°C and 25°C for 30 days, under accelerated conditions (40°C/75% RH) for up to 3 months, and after freeze–thaw and centrifugation stress.

3 Results and discussion

3.1 Pre-formulation screening and excipient selection

Bempedoic acid showed the greatest solubility among the screened solid lipids in Precirol® ATO 5 (34.2 ± 2.1 mg/g), followed by Compritol® 888 ATO (29.7 ± 1.8 mg/g). Among liquid lipids, Capryol® 90 provided the highest solubility (48.5 ± 3.2 mg/mL), followed by oleic acid (41.2 ± 2.6 mg/mL). These results supported selection of Precirol® ATO 5 and Capryol® 90 for the NLC matrix. The partition coefficient was 25.6 ± 1.9 (log P ≈ 1.41) for n-octanol/buffer and 31.8 ± 2.4 (log P ≈ 1.50) for the selected lipid phase/buffer, indicating preferential distribution into the lipid phase.

FTIR spectra retained the characteristic bempedoic acid bands, including O–H stretching near 3386 cm^{-1} and C=O stretching near 1719 cm^{-1}, without new diagnostic bands or major shifts in the physical mixture. The pure drug showed a sharp DSC melting endotherm at approximately 91.86°C; this measurement represents the pure-drug thermal baseline only. Surfactant screening showed that Tween® 80 + Poloxamer 188 provided the highest transmittance (94.0 ± 1.2%) and remained visually stable for 2 h. ANOVA indicated a significant difference among surfactant systems ($F(3,8) = 57.41$, $p < 0.001$).

3.2 Lipid ratio optimization and optimized composition

The effect of the solid-to-liquid lipid ratio is shown in Table 1.

Table 1. Effect of solid-to-liquid lipid ratio.

Ratio	Size (nm)	PDI	Zeta (mV)	24 h
90:10	198.5 ± 8.7	0.31 ± 0.02	−18.2 ± 1.4	Stable
80:20	152.4 ± 6.1	0.22 ± 0.01	−23.6 ± 1.8	Stable
70:30	171.9 ± 9.2	0.36 ± 0.03	−21.0 ± 1.6	Slight creaming

The 80:20 ratio produced the smallest particle size and lowest PDI among the tested blends, with no visible phase separation. Lipid ratio significantly affected particle size ($F(2,6) = 24.40$, $p = 0.0013$), PDI ($F(2,6) = 32.36$, $p = 0.00061$), and zeta potential ($F(2,6) = 8.46$, $p = 0.0179$). The 80:20 blend was the only candidate meeting all predefined constraints (particle size <200 nm, PDI ≤0.30, |zeta potential| ≥20 mV, and no phase separation at 24 h).

The composition of the optimized NLC dispersion is given in Table 2.

Table 2. Composition of the optimized NLC dispersion.

Component	Selected material	Concentration
Solid lipid	Precirol® ATO 5	2.4% w/v
Liquid lipid	Capryol® 90	0.6% w/v
Surfactant	Tween® 80	1.5% w/v
Co-stabilizer	Poloxamer 188	0.5% w/v
Drug	Bempedoic acid	0.2% w/v
Vehicle	Purified water	q.s.

3.3 Physicochemical and morphological characterization

The physicochemical properties of the optimized NLC are summarised in Table 3.

Table 3. Physicochemical properties of optimized NLC.

Parameter	Optimized NLC
Particle size	145.8 ± 4.9 nm
PDI	0.21 ± 0.02
Zeta potential	−24.7 ± 1.5 mV
Entrapment efficiency	86.3 ± 2.4%
Drug loading	4.6 ± 0.3%
Drug content	98.9 ± 1.7%

The optimized dispersion showed a narrow particle-size distribution and high drug entrapment. TEM revealed predominantly near-spherical nanoparticles with limited aggregation; SEM provided qualitative information on the dried particle surface and clustering. FTIR comparison of pure drug, blank NLC, and drug-loaded NLC showed no new bands indicative of chemical incompatibility. XRD showed reduced intensity and/or disappearance of characteristic sharp bempedoic acid reflections in

the loaded NLC, consistent with reduced crystalline order and drug incorporation within the lipid matrix.

3.4 In vitro drug release and release kinetics

The cumulative drug release in the pH-shift medium is presented in Table 4.

Table 4. Cumulative drug release in pH-shift medium.

Time (h)	Suspension (%)	NLC (%)
1	6.8 ± 0.9	18.4 ± 1.3
2	9.5 ± 1.1	26.7 ± 1.6
4	13.2 ± 1.4	39.8 ± 2.1
8	18.6 ± 1.8	55.4 ± 2.4
12	21.9 ± 2.0	66.1 ± 2.6
24	28.7 ± 2.2	79.3 ± 3.1

The NLC showed a biphasic release profile, with faster initial release followed by a sustained phase. At 24 h, cumulative release was 79.3 ± 3.1% for NLCs compared with 28.7 ± 2.2% for suspension. The Korsmeyer–Peppas model provided the best fit (R^2 = 0.989), followed by the Higuchi model (R^2 = 0.981); first-order and zero-order fits were lower (R^2 = 0.927 and 0.903, respectively). The release exponent (n = 0.52) was interpreted as anomalous, diffusion-dominant transport. The improved release is consistent with nanoscale dispersion, increased effective surface area, and maintenance of drug in a lipid–surfactant microenvironment.

3.5 Biorelevant in vitro lipolysis

Following pH-stat digestion and phase separation, 67.9 ± 3.4% of bempedoic acid from the optimized NLC was recovered in the micellar/aqueous fraction, compared with 24.6 ± 2.8% for the plain suspension. This finding indicates that the lipid carrier maintained a greater proportion of drug in a solubilized fraction during simulated intestinal digestion. The result supports improved digestion-phase solubilization, but does not by itself establish increased systemic bioavailability.

3.6 Stability assessment

Over 30 days, refrigerated storage better preserved the dispersion than storage at 25°C. At 4°C, particle size changed from 145.8 to 151.2 nm, PDI from 0.21 to 0.23, zeta potential from −24.7 to −23.9 mV, and drug content from 98.9% to 97.4%. At 25°C, particle size increased to 162.6 nm, PDI to 0.26, zeta potential changed to −22.8 mV, and drug content was 96.8%; no visible creaming, phase separation, or precipitation was observed. Under accelerated storage (40°C/75% RH), particle size increased to 214.7 ± 10.2 nm and PDI to 0.37 ± 0.04 by 3 months, while drug content decreased to 92.8 ± 2.6%. Freeze–thaw cycling caused modest size/PDI drift without visible separation; centrifugation caused minimal changes. These results indicate temperature-sensitive stability and support refrigerated storage for the aqueous dispersion.

4 Conclusion

A bempedoic acid-loaded aqueous NLC dispersion was successfully developed using a pre-formulation-guided, screening-based approach. The selected Precirol® ATO 5:Capryol® 90 (80:20) matrix, stabilized with Tween® 80 and Poloxamer 188, produced nanoparticles with a mean size of 145.8 ± 4.9 nm, PDI of 0.21 ± 0.02, and entrapment efficiency of 86.3 ± 2.4%. Compared with plain suspension, the optimized NLC improved pH-shift release and maintained a greater fraction of drug in the micellar/aqueous phase during in vitro lipolysis. Short-term stability was better at 4°C, whereas accelerated thermal storage caused particle growth and reduced drug content. The findings support the NLC dispersion as a promising formulation strategy to improve bempedoic acid release and intestinal solubilization. The study was limited to in vitro evaluation; pharmacokinetic studies, longer-term stability work, and development of a patient-ready dosage form are required before conclusions about clinical absorption or therapeutic performance can be made.

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