PHARMACEUTICS

Tofacitinib-Loaded Nanostructured Lipid Carriers: Formulation, Characterization and In Vitro Release

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Abstract

Background: Tofacitinib is an orally administered Janus kinase inhibitor. Nanostructured lipid carriers (NLCs) combine solid and liquid lipids and may alter drug dispersion, association and release in the gastrointestinal environment. This study examined a tofacitinib-loaded NLC system.

Methods: Candidate lipids and surfactants were screened, and five batches (F1–F5) containing glyceryl monostearate (solid lipid) and oleic acid (liquid lipid) were compared. Dispersions were prepared by high-pressure homogenization and/or ultrasonication. Particle size, polydispersity index (PDI), zeta potential and entrapment efficiency were measured; compatibility and solid-state behavior were examined by FTIR, DSC and XRD. In vitro release, three-month colloidal stability and a summarized oral pharmacokinetic comparison were evaluated.

Results: Batch F5 showed a mean particle size of 118.5 nm, PDI of 0.198, zeta potential of −32.1 mV and entrapment efficiency of 88.9%. Cumulative release at 24 h was 96.5% for F5 and 82.1% for pure drug, with the Higuchi model giving the best fit (R^2 = 0.987). After three months, particle size, entrapment efficiency and zeta potential changed from 118.5 to 125.2 nm, from 88.9% to 86.7% and from −32.1 to −30.4 mV, respectively. Reported Cmax values were 3.9 µg/mL (NLC) and 1.8 µg/mL (pure drug), and AUC values were 29.8 and 12.4 (units not stated).

Conclusion: A tofacitinib-containing NLC dispersion with favorable colloidal properties and greater in vitro release than pure drug was prepared. The pharmacokinetic difference is preliminary and requires confirmation with complete, dose-normalized data.

Keywords: in vitro release; nanostructured lipid carriers; oral delivery; pharmacokinetics; tofacitinib

1 Introduction

Oral administration remains a widely used route for long-term pharmacotherapy because it is convenient and generally avoids the procedural burden associated with injectable products. However, swallowing a dose does not ensure that the same fraction of unchanged drug reaches systemic circulation. Dissolution, luminal solubilization, epithelial transport, and presystemic metabolism can each influence oral exposure. Their relative importance is compound-specific and may vary with gastrointestinal conditions and formulation composition [1], [2].

Lipid-based formulations have been investigated for compounds whose delivery is affected by limited aqueous presentation or by changes in drug partitioning during gastrointestinal transit. After ingestion, formulation lipids encounter bile salts and digestive enzymes. The resulting fatty acids, monoglycerides, and colloidal structures may alter the distribution of drug between aqueous and lipid-associated phases. Whether this improves the amount available for absorption depends on the

drug, lipid composition, dilution, digestion, and precipitation behavior; it should not be assumed from the presence of lipid alone [1]–[3].

The Biopharmaceutics Classification System relates aqueous solubility and intestinal permeability to drug-product performance and provides a framework for identifying likely absorption constraints [4]. A formulation that increases apparent solubility may be useful when dissolution is limiting, but it will not necessarily overcome restricted epithelial permeability or presystemic clearance. Accordingly, solubility, release, permeability, and systemic exposure should be treated as related but distinct outcomes [4], [5].

1.1 Tofacitinib and formulation rationale

Tofacitinib is an orally administered small-molecule inhibitor of Janus kinase signaling. Its pharmacological action involves inhibition of JAK-family signaling, particularly JAK1 and JAK3, with activity against JAK2, thereby modifying cytokine-mediated signal transduction [6]. The drug is used in selected inflammatory disorders, including rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis, under indication-specific prescribing and safety requirements.

Human disposition studies describe absorption after oral administration and metabolism that includes CYP3A4-mediated pathways, alongside renal and hepatic clearance processes [7]. These characteristics make formulation performance and measured systemic exposure relevant, but they do not establish that tofacitinib is primarily dissolution-limited or that it is a P-glycoprotein substrate under the conditions used in this work. Nor do they prove that an NLC bypasses hepatic first-pass metabolism. Such mechanisms require direct, drug-specific experiments.

1.2 Nanostructured lipid carriers

NLCs combine a solid lipid with a liquid lipid in a dispersed particulate system. The liquid component can disrupt the regular packing of the solid lipid and may create a less ordered matrix that accommodates some drugs more effectively than a fully solid lipid core. Particle size, lipid ratio, surfactant composition, and processing conditions jointly influence the resulting dispersion, drug association, and release characteristics [3], [8].

Oral NLC studies involving raloxifene, silymarin, candesartan cilexetil, and simvastatin have reported changes in *in vitro* performance and systemic exposure, although the magnitude of benefit differs by drug and formulation [9]–[13]. These results provide a rationale for evaluating an NLC for tofacitinib; they are not a substitute for compound-specific evidence. A prior tofacitinib study described solid lipid nanoparticles rather than an oral NLC pharmacokinetic system [14].

1.3 Study rationale and objective

The present work investigated whether tofacitinib could be incorporated into a mixed-lipid carrier based on glyceryl monostearate and oleic acid, and whether the resulting dispersion exhibited measurable particle, entrapment, and release characteristics suitable for further oral formulation research. The objective was to compare the F1–F5 screening batches, identify the batch with the most favorable physicochemical responses, and summarize its *in vitro* release, short-term storage observations, and pharmacokinetic comparison.

The principal working hypothesis was that a solid–liquid lipid matrix stabilized with non-ionic surfactants could produce a nanoscale dispersion with substantial drug association. An improvement in solubilization or release was considered a formulation outcome to be measured. Enhanced

intestinal permeability, lymphatic transport, reduced first-pass metabolism, therapeutic superiority, and reduced dosing frequency were not treated as established outcomes.

2 Materials and methods

2.1 Materials

Tofacitinib was obtained from Sigma-Aldrich. Candidate solid lipids included glyceryl monostearate, stearic acid, and Compritol 888 ATO. Candidate liquid lipids included oleic acid, Capryol 90, and Miglyol 812. Tween 80 and Poloxamer 188 were evaluated as surfactant/stabilizing agents, while ethanol and propylene glycol were included among the co-solvent materials. Methanol, ethanol, and chloroform were of HPLC grade. Aqueous media at pH 1.2, 6.8, and 7.4 were prepared using analytical-grade reagents and distilled water.

2.2 Preformulation screening

For solubility screening, excess tofacitinib was added to distilled water, buffers at pH 1.2, 6.8, and 7.4, and selected lipid excipients. Samples were agitated for 48 h at 37 ± 0.5 °C. Undissolved material was separated by centrifugation at 10,000 rpm for 15 min and filtration through a 0.45-µm membrane. The drug concentration in the clarified fraction was determined spectrophotometrically at the absorption maximum. The reported values are treated as screening measurements, not as a formal BCS classification.

The melting interval was examined by a capillary method and DSC. The n-octanol/water partition coefficient was determined after equilibration of the two phases for 24 h, followed by concentration measurement in each phase. Drug–excipient compatibility was examined using FTIR spectra collected over 4000–400 cm^{-1}, DSC under nitrogen during controlled heating, and powder XRD. These methods were interpreted together as screening tools for changes in spectral, thermal, and crystalline behavior.

2.3 Lipid and surfactant selection

Candidate lipids were screened by adding excess drug to heated lipid materials under controlled conditions and examining apparent drug affinity. Surfactants were assessed for solubilization and dispersion behavior, including emulsion transmittance and visible phase separation. Glyceryl monostearate was selected as the solid matrix component and oleic acid as the liquid lipid, the latter showing the highest apparent solubilizing capacity among the evaluated liquid lipids. Tween 80 and Poloxamer 188 were retained to support formation and stabilization of the dispersion.

2.4 Preparation and screening of NLC batches

A drug-containing lipid phase was heated until molten. A separate aqueous surfactant phase was heated to a comparable temperature and combined with the lipid phase under stirring to form a coarse emulsion. The dispersion was processed by high-pressure homogenization within a range of 500–1500 bar and/or probe ultrasonication, followed by cooling to solidify the lipid phase. The selected process parameters were 1000 bar, five homogenization cycles, 10 min of sonication, a lipid-phase temperature of 70–75 °C, and rapid cooling.

Five formulations (F1–F5) were compared. Each contained 50 mg of tofacitinib per 100 mL, while the amounts of glyceryl monostearate, oleic acid, Tween 80, and Poloxamer 188 varied (Table 1). The

batches were treated as a formulation-screening series. Because they were not generated from a documented factorial or response-surface design and replicate-level data are not reported, causal effects of individual ingredients are not claimed.

Table 1. Composition of the five tofacitinib NLC screening batches.

Component	F1	F2	F3	F4	F5
Tofacitinib (mg/100 mL)	50	50	50	50	50
Glyceryl monostearate (g)	2.0	2.0	1.5	1.5	1.0
Oleic acid (g)	0.5	1.0	1.0	1.5	1.5
Tween 80 (% w/v)	1.0	1.5	1.5	2.0	2.5
Poloxamer 188 (% w/v)	0.5	0.5	1.0	1.0	1.5
Distilled water (to 100 mL)	q.s.	q.s.	q.s.	q.s.	q.s.

2.5 Physicochemical characterization

Hydrodynamic diameter and PDI were measured by dynamic light scattering using a Malvern Zetasizer at 25 °C and a 90° detection angle after dilution with distilled water. Zeta potential was determined from electrophoretic mobility using a diluted dispersion. Entrapment efficiency was estimated after centrifugation at 15,000 rpm for 30 min to separate the free-drug fraction; drug in the supernatant was quantified and associated drug was estimated by difference from the amount initially added.

TEM and SEM were used for qualitative morphological assessment. For DSC, samples were heated under nitrogen at 10 °C/min. XRD scans covered 2θ values from 5° to 80°. The interpretation of reduced drug-associated thermal or diffraction signals was cautious because excipient dilution and changes in sample composition can also influence signal intensity.

2.6 In vitro release, stability, and pharmacokinetic assessment

In vitro release was assessed using a dialysis-bag method. The membrane was conditioned overnight, and a measured portion of the NLC dispersion or pure-drug comparator was enclosed within it. The assembly was placed in release medium comprising pH 1.2 and pH 6.8 buffers, maintained at 37 ± 0.5 °C with stirring. Samples were withdrawn at designated time points and replaced with equal volumes of fresh medium. Drug concentrations were measured by UV spectroscopy or HPLC. Release data were compared with zero-order, first-order, Higuchi, and Korsmeyer–Peppas models.

Stability evaluation was referenced to ICH Q1A(R2), including 25 ± 2 °C/60 ± 5% relative humidity and 40 ± 2 °C/75 ± 5% relative humidity. F5 was followed for three months for particle size, entrapment efficiency, and zeta potential.

An oral comparison was performed in male Wistar rats (200–250 g) receiving pure drug or the NLC formulation. Blood was collected at 0, 1, 2, 4, 6, 8, 12, and 24 h. Plasma concentrations were determined using a validated HPLC or LC–MS method. C_{max}, T_{max}, AUC, and elimination half-life are presented as summary values.

2.7 Data handling

The screening results are summarized descriptively. No inferential statistical analysis is reported, and statistical significance was not assessed; accordingly, inferential claims are avoided.

3 Results

3.1 Preformulation findings

The apparent equilibrium concentration of tofacitinib was 0.42 mg/mL in distilled water, 0.58 mg/mL in pH 1.2 buffer, and 0.64 mg/mL in pH 6.8 buffer. The recorded lipid-screening values were 18.6 mg/mL in oleic acid, 15.2 mg/mL in Capryol 90, and 9.8 mg/g in glyceryl monostearate. Because the glyceryl monostearate result is expressed per gram while the other lipid values are expressed per milliliter, these values should not be compared as equivalent quantitative measures. The results nonetheless supported further investigation of a lipid-containing formulation.

The measured melting interval was approximately 146–148 °C. The n-octanol/water partition coefficient was log P = 2.3 ± 0.12. FTIR comparisons retained recognizable drug-associated absorption features in the physical mixtures, with no major incompatibility indicated. DSC showed broadening or attenuation of the drug-associated endotherm, while XRD showed reduced intensity of selected crystalline features. These observations are compatible with a changed thermal or solid-state environment, but do not independently prove complete amorphization or the location of drug inside the lipid particles.

3.2 Formulation screening and particle characterization

All five batches were homogeneous, milky-white dispersions without visible phase separation during preparation. Across the F1–F5 series, mean particle size decreased from 245.6 to 118.5 nm, while PDI declined from 0.312 to 0.198 (Table 2). The magnitude of the negative zeta potential increased from 18.5 to 32.1 mV, and entrapment efficiency rose from 68.4% to 88.9%. Because multiple composition variables changed simultaneously across the screening series, these trends cannot be attributed to a single excipient or used to establish ingredient-specific effects.

Table 2. Physicochemical responses of batches F1–F5.

Batch	Size (nm)	PDI	Zeta potential (mV)	EE (%)
F1	245.6	0.312	−18.5	68.4
F2	198.4	0.289	−22.3	74.2
F3	176.3	0.254	−26.7	80.5
F4	142.7	0.221	−29.4	85.6
F5	118.5	0.198	−32.1	88.9

Note: PDI, polydispersity index; EE, entrapment efficiency.

F5 had the smallest mean diameter and PDI, the largest absolute zeta potential, and the highest entrapment efficiency among the five batches. It was therefore selected for the subsequent release and stability assessments. The zeta-potential value is consistent with a substantial electrokinetic potential under the measurement conditions, although electrostatic values alone do not establish long-term stability, particularly in a surfactant-stabilized system.

3.3 Morphology and solid-state observations

TEM and SEM observations showed predominantly spherical particles with a smooth surface and relatively uniform appearance. The DSC thermogram showed attenuation and broadening of the drug-associated transition, and the XRD pattern showed reduced intensity of selected diffraction features. Together, these findings support altered physical organization in the NLC preparation.

3.4 In vitro release profile

Cumulative drug release was greater for F5 than for the pure-drug comparator at each time point (Table 3). At 1 h, release was 32.5% for F5 and 18.2% for pure drug; at 24 h, the corresponding values were 96.5% and 82.1%. The Higuchi model fit was R^2 = 0.987, which is consistent with a diffusional contribution under the assumptions of that model. It does not demonstrate that diffusion was the sole release mechanism.

Table 3. Cumulative in vitro release of pure tofacitinib and F5.

Time (h)	Pure drug (%)	F5 NLC (%)
1	18.2	32.5
4	34.6	58.7
8	52.3	76.4
12	68.5	88.2
24	82.1	96.5

The higher recovery of drug in the release medium may reflect differences in dispersion, drug partitioning, surfactant-mediated solubilization, or transport across the dialysis membrane. The experiment does not isolate these contributions. In addition, a higher *in vitro* cumulative release value should not be described as prolonged plasma exposure or as proof of a sustained clinical effect.

3.5 Three-month stability observations

The measured colloidal attributes of F5 changed modestly over the three-month interval (Table 4). Mean particle size increased from 118.5 to 125.2 nm, entrapment efficiency decreased from 88.9% to 86.7%, and zeta potential shifted from −32.1 to −30.4 mV. These data indicate limited change in the measured attributes over the observation period. They do not establish chemical stability, degradation-product control, shelf life, or stability under both ICH storage conditions because a complete assay dataset was not generated for each condition.

Table 4. Initial and three-month observations for F5.

Parameter	Initial	After 3 months
Particle size	118.5 nm	125.2 nm
Entrapment efficiency	88.9%	86.7%
Zeta potential	−32.1 mV	−30.4 mV

3.6 Pharmacokinetic summary

The summary values show higher C_{max} and AUC for the NLC group than for the pure-drug group (Table 5). C_{max} increased from 1.8 to 3.9 μg/mL, T_{max} shifted from 1.5 to 2.0 h, AUC increased from 12.4 to 29.8 (units not stated), and half-life increased from 3.2 to 6.1 h. The numerical AUC ratio is approximately 2.4 (29.8/12.4). This is described as an AUC ratio rather than confirmed relative bioavailability until the units, administered doses, sampling records, and underlying concentration–time data are verified.

Table 5. Pharmacokinetic parameters of pure drug and NLC F5 after oral administration in rats.

Parameter	Pure drug	NLC F5
C_{max}	1.8 μg/mL	3.9 μg/mL
T_{max}	1.5 h	2.0 h
AUC	12.4 μg·h/mL	29.8 μg·h/mL
t½	3.2 h	6.1 h

4 Discussion

This study provides preliminary evidence that tofacitinib can be formulated in a mixed-lipid nanoparticulate dispersion using glyceryl monostearate and oleic acid with Tween 80 and Poloxamer 188. The selected batch, F5, showed a mean diameter of 118.5 nm, a PDI of 0.198, and an entrapment efficiency of 88.9%. These results indicate successful preparation of a relatively narrow nanoscale dispersion with a high fraction of drug associated with the separated carrier phase under the assay conditions. They do not, by themselves, establish where the drug resides within the particle or whether intact nanoparticles cross the intestinal epithelium.

The preformulation screen showed higher apparent tofacitinib concentration in oleic acid and Capryol 90 than in the aqueous media tested. This observation supported testing of a lipid phase, consistent with the broader rationale for lipid-based oral formulations [1]–[3]. However, the differing units for the glyceryl monostearate and liquid-lipid measurements, as well as the absence of a validated saturation-solubility protocol, limit quantitative comparisons. The reported log P and aqueous measurements should likewise be considered study-specific screening data rather than a formal biopharmaceutical classification.

NLCs are designed to combine the structural contribution of a solid lipid with the packing-disrupting effect of a liquid lipid. The reduced intensity of selected XRD features and the changed DSC profile are compatible with a modified solid-state environment, but excipient dilution and matrix effects can also attenuate these signals. The study therefore supports an altered thermal/diffraction profile, not an unqualified assertion that tofacitinib became fully amorphous. Such interpretation is consistent with established descriptions of lipid nanoparticles and their characterization requirements [8].

The progressive decline in particle size and PDI and the rise in entrapment efficiency across F1–F5 are encouraging descriptive trends. Nevertheless, the batches changed in several variables at the same time. It is therefore not possible to infer that a higher oleic-acid, Tween 80, or Poloxamer 188 concentration independently caused the observed response. Proper optimization would require a documented experimental design, replicate measurements, model diagnostics, and confirmation batches.

The *in vitro* release profile showed higher cumulative drug recovery from F5 than from pure drug at all five time points. A Higuchi R^2 of 0.987 suggests that the data are compatible with a diffusion-related model over the tested interval. However, dialysis methods can reflect both release from the carrier and transport through the membrane, while surfactants may change the apparent solubilization capacity of the external medium. A discriminatory release method and suitable sink-condition evidence are needed before assigning a specific release mechanism. The profile should not be equated with extended therapeutic activity or a reduced dosing frequency.

In the literature, NLC formulations for raloxifene, silymarin, candesartan cilexetil, and simvastatin have reported improvements in selected oral exposure outcomes [9]–[13]. These studies demonstrate that oral NLC performance is formulation- and drug-dependent. Deepika and Naik [14] reported a tofacitinib citrate solid lipid nanoparticle system with a particle size of 181.5 nm and entrapment efficiency of 62.07%, but their system was not an oral NLC pharmacokinetic study. The present formulation therefore adds preliminary formulation-specific observations, while any comparison of bioavailability magnitude across compounds would be inappropriate.

4.1 Interpretation of stability and pharmacokinetic observations

The modest shifts in particle size, entrapment efficiency, and zeta potential over three months are compatible with short-term retention of selected colloidal properties. Stability should nevertheless be established using condition-specific records, validated assay of drug content and degradants, PDI, physical appearance, redispersibility where relevant, and replicate batches. The initial and final values cannot define a shelf life without the storage condition, packaging system, sample number, and complete data history.

The pharmacokinetic summary is potentially important because the AUC is approximately 2.4 times the reference value and C_{max} is higher for F5. However, an apparent half-life change can also reflect differences in sampling and estimation, and the dose, group size, and variability of the measurements bear directly on how far the result can be generalized. The result is therefore regarded as a hypothesis-generating comparison, not definitive proof of a 2.4-fold increase in oral bioavailability. Absolute bioavailability would require an appropriate intravenous reference; relative bioavailability requires matched doses and comparable study conditions.

4.2 Limitations

Several limitations apply. The five batches were a screening series rather than a designed experiment, so ingredient-specific effects cannot be assigned. Release was assessed by a dialysis method that is not necessarily discriminatory, and the stability data cover only particle size, entrapment efficiency, and zeta potential at a single reported condition, without assay of drug content or degradation products. The pharmacokinetic comparison is a summary of a single oral study without an intravenous reference, and its absolute and relative bioavailability implications are unestablished. Finally, the mechanisms invoked in the literature for lipid carriers (enhanced permeability, lymphatic transport, and reduced first-pass metabolism) were not tested here. Confirmation with replicated, fully documented physicochemical, stability, and pharmacokinetic datasets is required before translational conclusions are drawn.

5 Conclusion

A tofacitinib-containing NLC dispersion based on glyceryl monostearate and oleic acid was prepared with nanoscale size, narrow size distribution, and high entrapment efficiency, and it released more drug *in vitro* than pure tofacitinib. The pharmacokinetic summary favors the NLC group but is preliminary; confirmation with complete, dose-normalized and reproducible datasets is necessary before any bioavailability or therapeutic claim is made.

Abbreviations

AUC, area under the plasma concentration–time curve; C_{max}, maximum plasma concentration; DSC, differential scanning calorimetry; EE, entrapment efficiency; FTIR, Fourier-transform infrared spectroscopy; HPH, high-pressure homogenization; NLC, nanostructured lipid carrier; PDI, polydispersity index; P-gp, P-glycoprotein; XRD, X-ray diffraction.

Declarations

Conflict of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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