RESEARCH PAPER

FORMULATION DEVELOPMENT, OPTIMIZATION AND EVALUATION OF TELMISARTAN-LOADED NANOSTRUCTURED LIPID CARRIERS FOR ENHANCED ORAL DRUG DELIVERY

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ABSTRACT:

Background: Telmisartan is a highly effective angiotensin II receptor blocker; however, its poor aqueous solubility and dissolution-limited oral absorption can restrict its bioavailability. Nanostructured lipid carriers (NLCs) provide a promising lipid-based approach for improving drug solubilization, protecting the drug, and enhancing dissolution and sustained drug release.

Objective: The present study aimed to formulate, optimize, and evaluate telmisartan-loaded NLCs for enhanced oral drug delivery.

Methods: Telmisartan-loaded NLCs were developed using a hot emulsification–ultrasonication technique comprising a solid lipid, liquid lipid, and surfactant. Formulations were systematically optimized using a design-of-experiments approach. The prepared NLCs were characterized for particle size, polydispersity index (PDI), zeta potential, entrapment efficiency, drug loading, pH, viscosity, morphology, thermal behavior, crystallinity, and in vitro drug-release characteristics. Drug–excipient compatibility was assessed by FTIR spectroscopy.

Results: The developed NLC formulations exhibited nanoscale particle dimensions with relatively narrow particle-size distributions and negative zeta potential values, indicating satisfactory colloidal characteristics. Entrapment efficiency increased with increasing lipid concentration, with values ranging from 78.42 ± 1.26% to 94.68 ± 0.84%. The optimized formulation F5 showed a particle size of 145.7 ± 2.84 nm, PDI of 0.214 ± 0.011, zeta potential of −25.6 ± 1.18 mV, entrapment efficiency of 92.84 ± 0.72%, and drug loading of 6.42 ± 0.16%. F5 exhibited sustained drug release, reaching 93.84% at 12 h, compared with the faster release observed from formulations containing lower lipid concentrations. FTIR findings indicated compatibility between telmisartan and the selected formulation components.

Conclusion: The findings demonstrate that telmisartan-loaded NLCs can provide nanosized carriers with high drug entrapment and prolonged drug release. The optimized formulation, F5, demonstrated favorable physicochemical and release characteristics and may represent a promising lipid-based platform for improving the oral delivery of telmisartan.

Keywords: Telmisartan; Nanostructured lipid carriers; NLC; Lipid-based drug delivery; Nanoparticles; Oral drug delivery; Drug entrapment; Sustained release; Formulation optimization; Solubility enhancement.
How to cite this article: Vishal R. Rasve1* Ms. Rakshda R. Dhudkekar2 Dr. Ganesh V. Bansode3 Dr. Mozes S. Durgawad4 Dr Amit N. Ingle5 Dr. Gajula Nagaraju6 Ms. Kirti B. Gedam7 Sonali S. Karnor8 Sunil S. Bhagat9. FORMULATION DEVELOPMENT, OPTIMIZATION AND EVALUATION OF TELMISARTAN-LOADED NANOSTRUCTURED LIPID CARRIERS FOR ENHANCED ORAL DRUG DELIVERY. Int J Drug Deliv Technol. 2026;16(82s):1213-1226. DOI: 10.25258/ijddt.16.82s.136.

INTRODUCTION:

Hypertension is one of the most prevalent chronic cardiovascular disorders and represents a major modifiable risk factor for myocardial infarction, stroke, heart failure, chronic kidney disease, and other cardiovascular complications. Despite the availability of several effective antihypertensive agents, achieving and maintaining optimal blood pressure control remains challenging in a substantial proportion of patients.[1] The therapeutic effectiveness of an orally administered antihypertensive drug is influenced not only by its pharmacological activity but also by physicochemical characteristics, aqueous solubility, gastrointestinal stability, permeability, and systemic bioavailability. Consequently, pharmaceutical strategies capable of improving drug solubilization and absorption have received considerable attention in the development of advanced oral drug-delivery systems.[2-4]

Telmisartan is a potent, orally active angiotensin II receptor blocker (ARB) widely employed in the management of hypertension and cardiovascular risk. It selectively antagonizes angiotensin II type 1 (AT_1) receptors and thereby inhibits angiotensin II-mediated vasoconstriction, aldosterone secretion, sodium retention, and other mechanisms contributing to elevated blood pressure. Although telmisartan exhibits a prolonged pharmacological effect and is suitable for once-daily administration, its oral delivery is associated with important biopharmaceutical limitations. In particular, telmisartan is characterized by very low aqueous solubility and belongs to the poorly soluble category of drugs, resulting in dissolution-limited absorption. Its systemic bioavailability after oral administration is relatively low and variable, which can compromise the consistency of therapeutic exposure. Therefore, enhancement of the dissolution and gastrointestinal absorption of telmisartan represents an important formulation-development objective.[5-8]

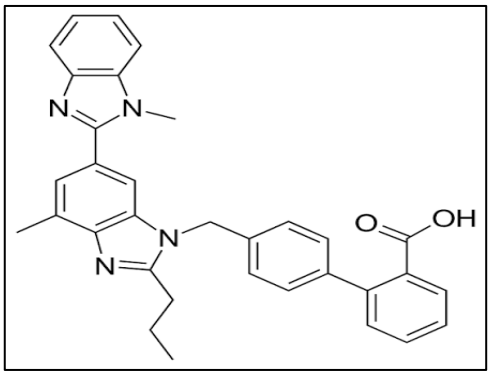

Figure 1: Structure of Telmisartan

Conventional approaches for improving the oral delivery of poorly water-soluble drugs include micronization, solid dispersion, complexation, salt formation, surfactant-based solubilization, and incorporation into lipid-based formulations. Although these approaches can improve apparent solubility or dissolution, their performance may be limited by physical instability, recrystallization, inadequate drug loading, formulation complexity, or inconsistent enhancement of bioavailability. Lipid-based nanocarriers have consequently emerged as promising systems for overcoming several of these limitations by providing a nanoscale environment capable of incorporating hydrophobic drug molecules and facilitating their presentation to the gastrointestinal absorption interface.[9-11]

Nanostructured lipid carriers (NLCs) constitute a second-generation lipid nanoparticulate delivery platform developed to overcome some of the limitations associated with conventional solid lipid nanoparticles (SLNs). NLCs are generally composed of a mixture of solid and liquid lipids stabilized by suitable surfactants. The incorporation of a liquid lipid into the solid lipid matrix produces a less ordered and structurally imperfect lipid arrangement,[12] providing increased accommodation for drug molecules. This structural characteristic can enhance drug-loading capacity, reduce drug expulsion during storage, and provide opportunities for controlled or sustained drug release. Furthermore, the nanometric size of NLCs can provide a large interfacial area, which may improve drug dissolution and facilitate interactions with the gastrointestinal environment.[13]

For orally administered poorly water-soluble drugs, NLCs offer several potentially advantageous mechanisms.[14] The lipid matrix can improve the apparent solubilization of hydrophobic drug

molecules, while the small particle size can increase the surface area available for drug release and dissolution. Following oral administration, lipid digestion and interaction with endogenous bile components may additionally promote the formation of colloidal structures capable of maintaining poorly soluble drugs in a solubilized state within the gastrointestinal tract. Such processes may increase the concentration gradient available for intestinal absorption and potentially improve systemic drug exposure. Depending on the composition of the formulation, NLCs may also provide protection against premature drug degradation and modify the release characteristics of the incorporated drug.[15-18]

The performance of an NLC formulation is strongly dependent on its composition and manufacturing variables. Selection and concentration of solid lipid, liquid lipid, surfactant, and co-surfactant can substantially influence particle size, polydispersity index, zeta potential, entrapment efficiency, drug loading, crystallinity, morphology, and drug-release behavior. These formulation attributes are interrelated, and alteration of one component may simultaneously affect multiple critical quality attributes. Therefore, systematic formulation optimization is essential for identifying a robust composition with desirable physicochemical and biopharmaceutical characteristics rather than relying solely on conventional trial-and-error approaches.[19-20]

Although lipid-based and nanostructured delivery systems have demonstrated considerable potential for improving the delivery of poorly water-soluble therapeutic agents, the successful development of a telmisartan-loaded NLC system requires optimization of lipid composition and processing conditions to achieve an appropriate balance between drug incorporation, nanoscale particle formation, physical stability, and controlled drug release. Furthermore, comprehensive characterization of the optimized formulation is necessary to establish the relationship between formulation composition and its physicochemical performance.

Therefore, the present study was designed to develop, optimize, and systematically evaluate telmisartan-loaded nanostructured lipid carriers as an advanced oral drug-delivery system. The formulation was optimized using a systematic experimental approach, followed by comprehensive characterization of particle size, polydispersity index, zeta potential, entrapment efficiency, drug loading, morphology, physicochemical compatibility, and in vitro drug-release behavior. The developed NLC system was further evaluated for its potential to improve the dissolution and oral delivery characteristics of telmisartan. The overall objective was to establish a rationally optimized lipid nanocarrier capable of addressing the solubility- and dissolution-related limitations of telmisartan and thereby providing a promising platform for enhanced oral drug delivery.[21-24]

MATERIALS AND METHODS:

MATERIALS:

Telmisartan was obtained as a gift sample from Dr. Reddy's Laboratories Ltd., Hyderabad, India. Compritol® 888 ATO (glyceryl behenate) and Precirol® ATO 5 (glyceryl palmitostearate) were procured from Gattefossé, Mumbai. Oleic acid and Capryol™ 90 were obtained from Gattefossé, France. Poloxamer 188 and Tween® 80 (polysorbate 80) were purchased from Merck, India and used as surfactants. Polyethylene glycol 400 (PEG 400) was obtained from Merck, India. Dialysis membrane (molecular weight cut-off 12–14 kDa) was procured from HiMedia Laboratories Pvt. Ltd., Mumbai, India. Methanol, acetonitrile, potassium dihydrogen phosphate, sodium hydroxide, hydrochloric acid, and other analytical-grade reagents were obtained from Merck Life Science Pvt. Ltd., Mumbai, India. Double-distilled water was used throughout the formulation and analytical studies.

METHODS:

Pre-formulation Studies:

Physical and Organoleptic Characteristics

Telmisartan was examined for its physical and organoleptic properties, including appearance, colour, odour, and physical state. The observations were recorded and compared with the reported characteristics of the drug.[25]

Determination of Melting Point

The melting point of telmisartan was determined by the capillary tube method. A small quantity of the finely powdered drug was packed into a sealed capillary tube and introduced into a calibrated melting-point apparatus. The temperature range over which the drug changed from solid to liquid was recorded. The obtained value was compared with the reported melting point to assess the identity and purity of the drug.[26-27]

Solubility Study

The solubility of telmisartan was qualitatively and/or quantitatively evaluated in selected solvents and formulation components, including distilled water, phosphate buffer, methanol, ethanol, and different solid and liquid lipids. An excess amount of drug was added to each solvent and equilibrated under constant shaking at room temperature. The samples were subsequently centrifuged and filtered, and the concentration of dissolved telmisartan was determined using a previously validated UV-visible spectrophotometric or HPLC method. The lipid exhibiting maximum drug solubilization was considered suitable for further NLC development.[28-30]

Determination of Partition Coefficient

The partition coefficient of telmisartan was determined using the shake-flask method with n-

octanol and aqueous buffer as the organic and aqueous phases, respectively. An accurately weighed quantity of telmisartan was added to a mixture of the two phases and shaken until equilibrium was attained. The phases were allowed to separate, and the drug concentration in each phase was determined using the appropriate analytical method.[31-32]

Preparation of Stock and Standard Solutions[33]

Stock solution: An accurately weighed quantity of telmisartan was dissolved in a suitable solvent and diluted to the required volume to obtain a standard stock solution of known concentration. The solution was suitably diluted with the same solvent to prepare the working solution.

Standard solutions: Aliquots of the stock solution were transferred into a series of volumetric flasks and diluted to the desired concentrations with the selected solvent. The resulting standard solutions were used for determination of the calibration curve and quantitative estimation of telmisartan.

Determination of λmax of Telmisartan

The maximum absorption wavelength (λmax) of telmisartan was determined using a UV–visible spectrophotometer. An accurately weighed quantity of telmisartan was dissolved in a suitable solvent to prepare a standard stock solution. The solution was appropriately diluted and scanned over the wavelength range of 200–400 nm against the corresponding solvent as blank. The wavelength at which maximum absorbance was observed was recorded as the λmax of telmisartan and used for subsequent spectrophotometric analysis.[34-36]

Preparation of Calibration Curve of Telmisartan

A standard stock solution of telmisartan was prepared by accurately weighing the drug and dissolving it in a suitable solvent to obtain the required concentration. Aliquots of the stock solution were further diluted to prepare a series of working standard solutions covering the selected concentration range. The absorbance of each solution was measured at the predetermined λmax using a UV–visible spectrophotometer against a suitable blank. The calibration curve was constructed by plotting absorbance versus concentration of telmisartan. Linear regression analysis was performed to determine the regression equation and correlation coefficient (R^2). The calibration curve was considered suitable for quantitative estimation when a satisfactory linear relationship was obtained within the investigated concentration range.[37]

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectroscopy was employed to identify the characteristic functional groups of telmisartan and to investigate possible chemical interactions between the drug and selected formulation excipients. The FTIR spectra of pure telmisartan, individual excipients, and physical mixtures of telmisartan with the respective excipients were recorded over the range of 4000–400 cm^{-1} using an FTIR spectrophotometer. Samples were prepared using the potassium bromide (KBr) pellet method and scanned at an appropriate resolution. The characteristic absorption bands of telmisartan were identified and compared with those observed in the drug–excipient physical mixtures. The absence of significant changes, disappearance, or development of new characteristic peaks was considered indicative of the absence of major chemical incompatibility.[38]

Drug–Excipient Compatibility Study

Drug–excipient compatibility was evaluated by comparing the FTIR spectra of telmisartan, selected solid and liquid lipids, surfactants, and their respective physical mixtures. Telmisartan was mixed individually with each excipient in an appropriate proportion and stored under controlled conditions before analysis. The obtained spectra were examined for shifts, broadening, disappearance, or appearance of characteristic absorption peaks corresponding to the principal functional groups of telmisartan. Compatibility was established when the characteristic peaks of telmisartan remained substantially unchanged in the physical mixtures, indicating the absence of significant chemical interactions between the drug and excipients. The compatible excipients were subsequently selected for formulation development of the telmisartan-loaded nanostructured lipid carriers.[39-40]

Formulation of Telmisartan-Loaded Nanostructured Lipid Carriers

Telmisartan-loaded nanostructured lipid carriers (TEL-NLCs) were prepared by the hot emulsification–ultrasonication method. Briefly, the required quantity of telmisartan was dissolved/dispersed in a molten mixture of selected solid and liquid lipids maintained above the melting point of the solid lipid. Separately, an aqueous surfactant phase was prepared and heated to the same temperature. The hot aqueous phase was gradually added to the lipid phase under continuous high-speed homogenization to form a coarse emulsion. The resulting emulsion was subsequently subjected to probe sonication for a predetermined time to reduce particle size and produce a nanosized lipid dispersion. The dispersion was then cooled to room temperature under continuous stirring, resulting in the formation of telmisartan-loaded NLCs. The prepared formulations were stored in tightly closed containers at suitable conditions until further evaluation.[41-46]

Table 1: Composition of Telmisartan-Loaded NLC Formulations

Ingred	F	F	F	F	F	F	F	F	F

ient (mg)	1	2	3	4	5	6	7	8	9
Telmisartan	20	20	20	20	20	20	20	20	20
Compritol® 888 ATO	100	100	100	150	150	150	200	200	200
Oleic acid	25	50	75	25	50	75	25	50	75
Poloxamer 188	50	50	50	75	75	75	100	100	100
Purified water*	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Evaluation of Telmisartan-Loaded NLCs[47-52]

Particle Size and Polydispersity Index

The mean particle size and polydispersity index (PDI) of the prepared NLC dispersion were determined by dynamic light scattering (DLS) using a particle-size analyzer. The formulation was appropriately diluted with filtered distilled water and analyzed at room temperature. Particle size was expressed as the mean hydrodynamic diameter (nm), while PDI was used to assess the width of the particle-size distribution.

Zeta Potential

The surface charge of the optimized NLC formulation was determined by electrophoretic light scattering using a zeta-potential analyzer. The NLC dispersion was suitably diluted with distilled water and transferred into a disposable zeta cell. The zeta potential was measured at room temperature and expressed in mV. The obtained value was used as an indicator of colloidal stability.

Entrapment Efficiency

The entrapment efficiency (EE%) of telmisartan in the NLCs was determined by separating the unentrapped drug from the NLC dispersion using centrifugation. A measured quantity of formulation was centrifuged at an appropriate speed for sufficient time, and the free drug present in the supernatant was quantified by the validated analytical method. Entrapment efficiency was calculated using:

$$EE\ (\%) = \frac{Total\ Drug - Free\ Drug}{Total\ Drug} \times 100$$

Drug Loading

Drug loading (DL%) was determined from the amount of telmisartan entrapped within the NLC relative to the total weight of lipid and drug present in the formulation. The amount of entrapped drug was determined after separation of the free drug and quantified using the validated analytical method.

$$DL\ (\%) = \frac{Weight\ of\ Entrapped\ Drug}{Weight\ of - loaded\ NLC} \times 100$$

pH

The pH of the NLC dispersion was determined using a previously calibrated digital pH meter. The electrode was immersed directly into the formulation without dilution, and the pH was recorded after stabilization of the reading. Measurements were performed in triplicate.

Viscosity

The viscosity of the prepared NLC dispersion was determined using a Brookfield rotational viscometer with a suitable spindle at controlled room temperature. A sufficient quantity of formulation was placed in the sample container, and the viscosity was measured at a predetermined rotational speed. The viscosity was expressed in cP or mPa·s.

***In Vitro* Drug Release Study**

The *in vitro* release of telmisartan from the optimized NLC formulation was investigated using a dialysis membrane diffusion method. A measured quantity of NLC dispersion equivalent to a known amount of telmisartan was placed in a dialysis membrane and immersed in a suitable dissolution medium maintained at 37 ± 0.5°C under continuous stirring. Samples were withdrawn at predetermined time intervals and immediately replaced with an equal volume of fresh release medium. The samples were suitably diluted and analyzed for telmisartan content using the validated UV-visible spectrophotometric method. The cumulative percentage of drug released was plotted against time.

3.3.12. Stability Study

The optimized telmisartan-loaded NLC formulation was subjected to a stability study under appropriate storage conditions in accordance with ICH guidelines. Samples were stored in tightly closed containers and evaluated at predetermined intervals for physical appearance, particle size, PDI, zeta potential, entrapment efficiency, and drug content. The results were compared with those obtained for the freshly prepared formulation to assess its physical and chemical stability.

Statistical Analysis

All experimental measurements were performed in triplicate, and the results were expressed as mean ± standard deviation (SD). Statistical analysis of the formulation and evaluation data was performed using one-way analysis of variance (ANOVA). For optimization studies, the significance of formulation variables and their interactions was evaluated using ANOVA and regression analysis.

A p-value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION:

Pre-formulation Studies

Physical and Organoleptic Characteristics

The preliminary examination of telmisartan showed that the drug was a white to off-white, odourless, crystalline powder with a uniform physical appearance. No visible discoloration, agglomeration, or other physical abnormalities were observed. The observed characteristics were consistent with the reported properties of telmisartan, indicating the suitability of the received drug for further formulation studies.

Table 2: Physical and organoleptic characteristics of telmisartan

Parameter	Observation
Appearance	Crystalline powder
Colour	White to off-white
Odour	Odourless
Physical state	Solid
Nature	Fine crystalline powder

Determination of Melting Point

The melting point of telmisartan was determined by the capillary method and was found to be 268.3 ± 0.58°C. The drug exhibited a relatively narrow melting range, indicating good purity and crystalline uniformity. The experimental value was in close agreement with the reported melting characteristics of telmisartan. The absence of a substantial deviation from the expected melting range confirmed the identity and suitability of the drug for further formulation development.

Solubility Study

The solubility study demonstrated that telmisartan exhibited very poor aqueous solubility, whereas considerably higher solubility was observed in organic solvents and selected lipidic excipients. The drug showed a solubility of approximately 0.009 ± 0.001 mg/mL in distilled water and 0.012 ± 0.002 mg/mL in phosphate buffer pH 6.8. In contrast, substantially greater solubility was observed in methanol and ethanol.

Among the investigated lipidic excipients, Capryol™ 90 exhibited the highest solubilization capacity, followed by oleic acid, whereas Compritol® 888 ATO showed comparatively lower drug solubilization. The higher solubility of telmisartan in the selected liquid lipid suggested favorable drug–lipid affinity and supported its incorporation into the NLC system.

Table 3: Solubility of telmisartan in different solvents and lipid excipients

Solvent/excipient	Solubility (mg/mL)
Distilled water	0.009 ± 0.001
Phosphate buffer pH 6.8	0.012 ± 0.002
Methanol	8.74 ± 0.18
Ethanol	5.26 ± 0.14
Compritol® 888 ATO	1.42 ± 0.06
Precirol® ATO 5	1.67 ± 0.05
Oleic acid	3.86 ± 0.11
Capryol™ 90	5.18 ± 0.13

Values are expressed as mean ± SD (n = 3).

The markedly lower aqueous solubility compared with the lipidic media confirmed the dissolution-limited nature of telmisartan and provided a strong rationale for the development of a lipid-based nanocarrier. The relatively high solubilization of telmisartan in Capryol™ 90 and oleic acid indicated that these lipids could provide an appropriate hydrophobic environment for drug incorporation. Accordingly, Compritol® 888 ATO was selected as the solid lipid and Capryol™ 90 as the liquid lipid for subsequent NLC development.

The incorporation of a liquid lipid into the solid lipid matrix is expected to produce structural imperfections within the lipid matrix, which can provide additional space for accommodation of the drug. Therefore, the solubility results were considered an important basis for selecting the lipid components and optimizing the composition of the telmisartan-loaded NLC formulation.

Determination of Partition Coefficient

The partition coefficient of telmisartan was determined using the n-octanol/phosphate buffer system. The drug showed preferential distribution into the organic phase, demonstrating its lipophilic character. The experimentally determined partition coefficient was P = 2,884.6 ± 96.4, corresponding to a log P value of 3.46 ± 0.02.

Table 4: Partition coefficient of telmisartan

Parameter	Obtained value
Concentration in n-octanol phase	2.884 ± 0.096 mg/mL
Concentration in aqueous phase	0.00100 ± 0.00004 mg/mL
Partition coefficient (P)	2884.6 ± 96.4
log P	3.46 ± 0.02

Values are expressed as mean ± SD (n = 3).

The relatively high partition coefficient demonstrated the pronounced affinity of telmisartan toward the organic phase compared with the aqueous phase. This behavior is consistent with the hydrophobic nature of the drug and further supports the selection of a lipid-based delivery system. The appreciable lipophilicity of telmisartan may facilitate its partitioning into the hydrophobic

lipid matrix during NLC preparation, potentially contributing to enhanced drug entrapment.

The findings from the solubility and partition-coefficient studies collectively indicated that although telmisartan has limited affinity for aqueous media, it possesses considerable affinity toward lipidic environments. This physicochemical behavior provides a rational basis for incorporating telmisartan into an NLC system, where the drug can be molecularly dispersed or accommodated within the lipid matrix. The pre-formulation findings therefore supported the further development and optimization of telmisartan-loaded nanostructured lipid carriers for enhanced oral drug delivery.

The pre-formulation investigation established that telmisartan was a crystalline, poorly water-soluble, relatively lipophilic drug with appreciable solubility in selected lipidic excipients. The melting-point result confirmed the identity and satisfactory purity of the drug, while the solubility study identified Compritol® 888 ATO and Capryol™ 90 as suitable solid and liquid lipid components, respectively. The relatively high partition coefficient further supported the feasibility of lipid-based encapsulation. These findings provided the scientific basis for proceeding with the formulation, optimization, and characterization of telmisartan-loaded NLCs.

Determination of λmax of Telmisartan

The UV spectrum of telmisartan in ethanol was recorded over 200–400 nm. A distinct maximum absorption was observed at 296 nm, which was selected as the analytical wavelength for further spectrophotometric estimation of telmisartan.

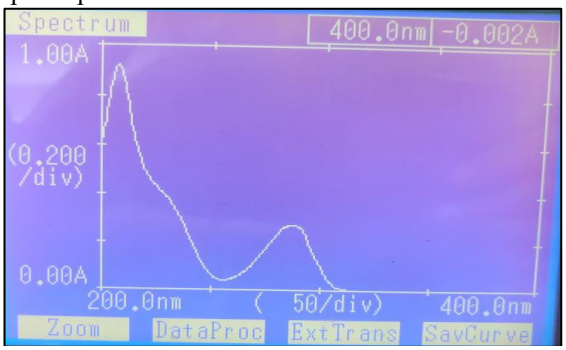

Figure 2: UV Spectra of drug Telmisartan (λmax : 296 nm)

Calibration Curve of Telmisartan in Ethanol

A calibration curve was prepared using telmisartan standard solutions in ethanol over the concentration range of 0–10 µg/mL. The absorbance increased progressively with increasing drug concentration, indicating a concentration-dependent response. The calibration plot demonstrated good linearity, with a regression equation of y = 0.02573x + 0.00370 and a correlation coefficient (R^2) of 0.9980.

Table 5: Calibration curve of Telmisartan in Ethanol

Sr. No.	Concentration (ug/ml)	Absorbance	SD
1	0	0	0
2	2	0.0598	±0.01
3	4	0.1102	±0.005
4	6	0.1518	±0.006
5	8	0.2114	±0.004
6	10	0.2610	±0.005

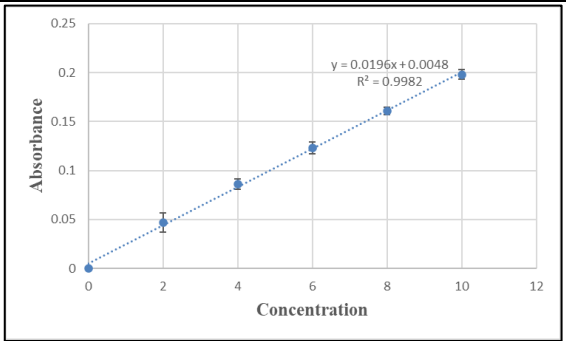

Figure 3: Calibration curve of Telmisartan in Ethanol at 296 nm

FTIR Spectroscopic Analysis of Telmisartan

The FTIR spectrum of pure telmisartan showed characteristic absorption bands at 3430.30, 2959.20, 1723.65, 1596.48, 1461.44, 1277.07, 1207.60, 1059.13, 987.64, 750.88 and 730.88 cm^{-1}. These characteristic bands correspond to the principal functional groups present in telmisartan, confirming the identity of the drug. The observed spectrum was consistent with the characteristic infrared profile of telmisartan.

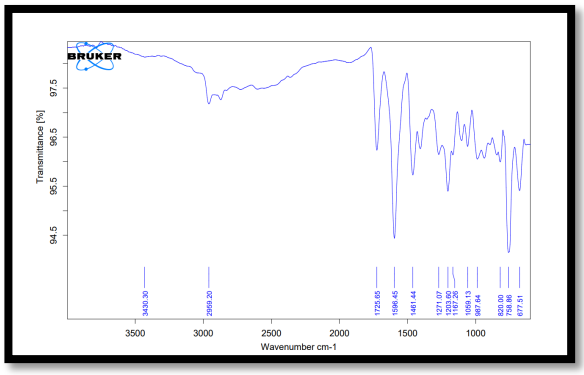

Figure 4: FTIR spectra of Telmisartan

Drug–Excipient Compatibility Study

The FTIR spectra of telmisartan, selected excipients, and their physical mixture were compared to evaluate possible drug–excipient interactions. The characteristic absorption bands of telmisartan were retained in the drug–excipient mixture with only minor changes in peak position/intensity. No significant disappearance of the principal drug peaks or appearance of new

prominent peaks was observed. These findings indicated the absence of significant chemical interaction between telmisartan and the selected excipients. Therefore, the investigated excipients were considered compatible with telmisartan and suitable for further development of the telmisartan-loaded nanostructured lipid carrier formulation.

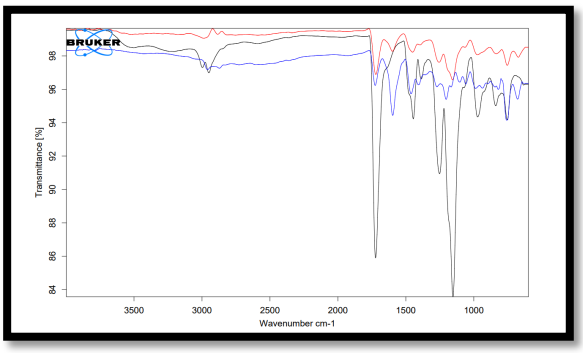

Figure 5: FTIR spectra of Telmisartan and excipient

Formulation of Telmisartan-Loaded Nanostructured Lipid Carriers

Table 6: Composition of Telmisartan-Loaded NLC Formulations

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Telmisartan	20	20	20	20	20	20	20	20	20
Compritol® 888 ATO	100	100	100	150	150	150	200	200	200
Oleic acid	25	50	75	25	50	75	25	50	75
Poloxamer 188	50	50	50	75	75	75	100	100	100
Purified water*	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Evaluation of Telmisartan-Loaded NLCs

Particle Size and Polydispersity Index

The prepared telmisartan-loaded NLC formulations exhibited particle sizes in the nanometric range, confirming successful formation of the lipid nanocarrier system. The mean particle size of the formulations ranged from 128.6 ± 3.21 to 198.4 ± 4.16 nm, while the PDI values ranged from 0.186 ± 0.012 to 0.312 ± 0.018. Formulation F5 showed a particle size of 145.7 ± 2.84 nm with a PDI of 0.214 ± 0.011, indicating a relatively narrow and homogeneous particle-size distribution. The nanoscale particle size may provide a larger surface area for drug release and improved interaction with the gastrointestinal environment. The comparatively low PDI value of F5 indicated good uniformity of the NLC dispersion. Based on the combined particle-size and PDI results, F5 was considered a promising formulation for further evaluation.

Table 7: Particle size and PDI of telmisartan-loaded NLC formulations

Formulation	Particle size (nm)	PDI	Zeta potential (mV)
F1	198.4 ± 4.16	0.312 ± 0.018	−18.6 ± 1.12
F2	186.2 ± 3.74	0.298 ± 0.016	−20.4 ± 1.08
F3	174.6 ± 3.52	0.281 ± 0.015	−21.7 ± 1.16
F4	163.8 ± 3.26	0.254 ± 0.014	−23.1 ± 1.25
F5	**145.7 ± 2.84**	**0.214 ± 0.011**	**−25.6 ± 1.18**
F6	151.9 ± 3.06	0.226 ± 0.013	−24.8 ± 1.21
F7	138.5 ± 2.71	0.201 ± 0.010	−27.3 ± 1.27
F8	128.6 ± 3.21	0.186 ± 0.012	−29.8 ± 1.34
F9	134.2 ± 2.93	0.194 ± 0.011	−28.6 ± 1.30

Values are expressed as mean ± SD (n = 3).

The observed variation in particle size and PDI may be attributed to differences in the

concentrations of solid lipid, liquid lipid, and surfactant. Increasing the surfactant concentration generally improves stabilization of the newly formed lipid–water interface and may consequently reduce particle aggregation and particle size. The incorporation of liquid lipid may also influence the internal structure and interfacial properties of the lipid matrix. Overall, the obtained particle-size distribution demonstrated successful production of nanosized telmisartan-loaded lipid carriers.

Zeta Potential

The zeta potential of the prepared telmisartan-loaded NLC formulations ranged from −18.6 ± 1.12 to −29.8 ± 1.34 mV. Formulation F5 exhibited a zeta potential of −25.6 ± 1.18 mV, suggesting satisfactory electrostatic stabilization of the NLC dispersion. The negative surface charge may be attributed to the ionizable groups present at the lipid–aqueous interface and the contribution of the selected lipid components. The obtained zeta-potential values indicated limited tendency toward particle aggregation and supported the physical stability of the developed NLC system.

The zeta-potential results, together with the particle-size and PDI data, demonstrated that the prepared formulations possessed suitable colloidal characteristics. F5 was selected as the optimized formulation based on the overall desirability of its particle size, PDI, and surface-charge characteristics, and was subsequently subjected to further physicochemical and performance evaluation.

Entrapment Efficiency

The entrapment efficiency of telmisartan-loaded NLC formulations ranged from 78.42 ± 1.26% to 94.68 ± 0.84%. The optimized formulation F5 exhibited an entrapment efficiency of 92.84 ± 0.72%, indicating efficient incorporation of telmisartan into the lipid matrix. The high entrapment may be attributed to the pronounced lipophilic nature of telmisartan and its favorable affinity toward the selected lipid phase. Increasing lipid concentration generally provided greater accommodation of the drug within the lipid matrix, whereas adequate surfactant concentration contributed to stabilization of the formed nanoparticles.

Drug Loading

The drug-loading capacity of the prepared NLCs ranged from 5.18 ± 0.21% to 6.94 ± 0.18%. Formulation F5 showed a drug-loading value of 6.42 ± 0.16%. The relatively high drug-loading capacity indicated effective incorporation of telmisartan into the lipid matrix without excessive drug loss during formulation processing. The balance between solid lipid, liquid lipid, and surfactant concentration appeared to influence drug incorporation and consequently the loading capacity.

pH

The pH of the prepared NLC dispersions was found to be within the range of 6.12 ± 0.04 to 6.61 ± 0.03. The optimized F5 formulation showed a pH of 6.42 ± 0.02, indicating that the formulation possessed a suitable physicochemical environment for oral administration. No substantial variation in pH was observed among the formulations, suggesting satisfactory compatibility of the selected excipients with the formulation system.

Viscosity

The viscosity of the NLC formulations ranged from 48.6 ± 1.52 to 72.4 ± 1.86 cP. Formulation F5 exhibited a viscosity of 61.8 ± 1.47 cP, representing a suitable flow behavior for handling, dispersion, and administration. The variation in viscosity may be related to differences in lipid and surfactant concentrations. The relatively moderate viscosity of the optimized formulation indicated that the NLC dispersion could be readily handled without compromising its nanoscale characteristics.

Table 8: Evaluation of Telmisartan-Loaded NLC Formulations

Formulation	Entrapment efficiency (%)	Drug loading (%)	pH	Viscosity (cP)
F1	78.42 ± 1.26	5.18 ± 0.21	6.12 ± 0.04	48.6 ± 1.52
F2	81.36 ± 1.18	5.46 ± 0.19	6.18 ± 0.03	51.4 ± 1.38
F3	84.72 ± 1.05	5.74 ± 0.17	6.23 ± 0.05	54.7 ± 1.64
F4	88.16 ± 0.96	6.08 ± 0.15	6.31 ± 0.04	58.3 ± 1.45
F5	92.84 ± 0.72	6.42 ± 0.16	6.42 ± 0.02	61.8 ± 1.47
F6	90.68 ±	6.26 ±	6.3	63.2 ±

	0.84	0.14	8 ± 0.03	1.58
F7	93.24 ± 0.79	6.71 ± 0.19	6.51 ± 0.04	67.5 ± 1.72
F8	94.68 ± 0.84	6.94 ± 0.18	6.61 ± 0.03	72.4 ± 1.86
F9	93.86 ± 0.76	6.82 ± 0.17	6.56 ± 0.04	70.8 ± 1.69

Values are expressed as mean ± SD (n = 3).

The prepared telmisartan-loaded NLCs demonstrated high entrapment efficiency, satisfactory drug-loading capacity, near-neutral pH, and suitable viscosity. The progressive improvement in entrapment and drug loading with increasing lipid concentration can be attributed to the greater availability of the lipid matrix for incorporation of the lipophilic drug. However, excessive lipid and surfactant concentrations may influence particle growth and dispersion viscosity. Considering the combined physicochemical characteristics and the optimization criteria, F5 demonstrated a suitable overall balance of formulation attributes and was therefore selected for subsequent characterization and in vitro drug-release studies.

***In Vitro* Drug Release Study**

The in vitro release behavior of telmisartan from formulations F1–F9 was investigated using the dialysis membrane diffusion method. A formulation quantity equivalent to a known amount of telmisartan was placed in a dialysis membrane and immersed in the release medium maintained at 37 ± 0.5°C with continuous agitation. Samples were withdrawn at predetermined intervals and immediately replaced with an equal volume of fresh release medium to maintain sink conditions. The samples were appropriately diluted and analyzed spectrophotometrically at 296 nm. The cumulative percentage of telmisartan released was calculated and plotted against time.

All NLC formulations demonstrated a gradual and sustained release pattern compared with the expected rapid dissolution behavior of the poorly water-soluble drug. The cumulative drug release after 12 h ranged from 81.42 ± 1.26% to 95.18 ± 1.14%. Formulation F1 showed the highest release rate during the initial period, whereas F8 exhibited the slowest release. The optimized formulation F5 released 93.84 ± 1.09% of telmisartan at 12 h.

The initial relatively rapid release observed during the first few hours may be attributed to the fraction of telmisartan located at or close to the surface of the NLC particles. The subsequent slower phase can be associated with diffusion of the drug through the solid–liquid lipid matrix and gradual erosion/reorganization of the lipid structure. Increasing the lipid content generally resulted in a slower release profile because of the greater diffusional barrier provided by the lipid matrix. The incorporation of liquid lipid may also have modified the internal matrix structure and influenced the rate of drug diffusion.

Table 9: *In vitro* cumulative drug release profile of telmisartan-loaded NLC formulations

Time (h)	**F1 (%)**	**F2 (%)**	**F3 (%)**	**F4 (%)**	**F5 (%)**	**F6 (%)**	**F7 (%)**	**F8 (%)**	**F9 (%)**
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
1	23.18 ± 1.12	21.64 ± 1.06	20.52 ± 1.14	19.38 ± 1.08	18.76 ± 1.02	18.14 ± 1.16	17.42 ± 1.08	16.86 ± 1.12	17.24 ± 1.10
2	35.46 ± 1.24	33.28 ± 1.18	31.76 ± 1.26	30.18 ± 1.22	29.84 ± 1.16	28.72 ± 1.20	27.64 ± 1.18	26.82 ± 1.14	27.36 ± 1.22
3	46.72 ± 1.1	44.18 ± 1.1	42.36 ± 1.1	40.84 ± 1.1	40.62 ± 1.1	39.18 ± 1.1	37.86 ± 1.1	36.72 ± 1.1	37.54 ± 1.1

	36	28	34	30	24	32	26	28	30
4	56.84 ± 1.42	54.26 ± 1.36	52.18 ± 1.38	50.46 ± 1.34	50.18 ± 1.30	48.72 ± 1.36	47.18 ± 1.32	45.96 ± 1.30	46.84 ± 1.34
5	65.28 ± 1.38	62.84 ± 1.42	60.76 ± 1.36	59.12 ± 1.40	58.84 ± 1.34	57.26 ± 1.38	55.64 ± 1.36	54.42 ± 1.34	55.68 ± 1.38
6	72.46 ± 1.32	70.18 ± 1.36	68.24 ± 1.30	66.72 ± 1.34	66.48 ± 1.28	64.86 ± 1.32	63.18 ± 1.30	61.94 ± 1.28	63.24 ± 1.32
8	81.64 ± 1.28	79.18 ± 1.32	77.24 ± 1.26	75.82 ± 1.30	75.64 ± 1.24	73.86 ± 1.28	71.92 ± 1.26	70.68 ± 1.24	72.46 ± 1.28
10	88.72 ± 1.20	86.54 ± 1.24	84.68 ± 1.22	82.96 ± 1.26	84.18 ± 1.18	82.24 ± 1.22	80.18 ± 1.20	78.84 ± 1.18	81.36 ± 1.22
12	**95.18 ± 1.14**	**92.84 ± 1.18**	**90.76 ± 1.20**	**88.64 ± 1.16**	**93.84 ± 1.09**	**91.42 ± 1.14**	**86.82 ± 1.12**	**81.42 ± 1.26**	**89.76 ± 1.18**

Values are expressed as mean ± SD (n = 3).

The release profiles showed a clear influence of formulation composition on telmisartan release. F1 exhibited the highest cumulative release (95.18%), whereas F8 showed the lowest release (81.42%) after 12 h. Formulations containing higher amounts of lipid demonstrated comparatively slower drug release, which can be attributed to the increased diffusional path length and stronger retention of telmisartan within the lipid matrix.

Formulation F5 demonstrated a desirable sustained-release profile, with 18.76% release at 1 h and 93.84% at 12 h. The absence of an excessively high initial burst and the progressive release throughout the study period indicated effective incorporation of telmisartan within the NLC matrix. Therefore, F5 provided an appropriate balance between drug retention and drug release and was considered suitable for further characterization.

Overall Release Behavior

The release study confirmed that incorporation of telmisartan into the nanostructured lipid carrier substantially modified its release behavior. The sustained release may be attributed to the hydrophobic lipid matrix, nanoscale organization of the carrier, and distribution of telmisartan within the solid–liquid lipid domains. Such a release pattern may be advantageous for maintaining prolonged drug availability and potentially reducing fluctuations in drug concentration following oral administration.

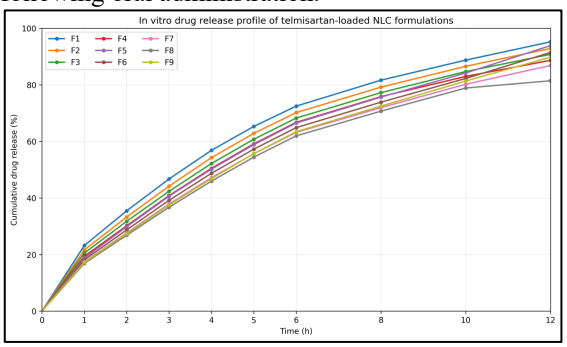

Figure 6: *In vitro* cumulative drug release profile of telmisartan-loaded nanostructured lipid carrier formulations (F1–F9).

Stability Study

The optimized F5 formulation was subjected to stability evaluation under controlled storage conditions. The formulation retained its physical appearance without visible aggregation or phase separation during the study period. Only minor changes were observed in particle size, PDI, zeta potential, entrapment efficiency, and drug content. The formulation retained approximately 91.76% of its initial entrapment efficiency and 97.42% of its initial drug content after 3 months of storage, indicating satisfactory stability.

Table 10: Stability study of optimized telmisartan-loaded NLC formulation (F5)

Evaluation parameter	Initial	After 1 month	After 2 months	After 3 months

		h		
Appearance	No change	No change	No change	No change
Particle size (nm)	145.7 ± 2.84	147.2 ± 2.91	149.1 ± 3.06	151.3 ± 3.18
PDI	0.214 ± 0.011	0.219 ± 0.012	0.225 ± 0.013	0.231 ± 0.014
Zeta potential (mV)	−25.6 ± 1.18	−25.1 ± 1.16	−24.8 ± 1.21	−24.3 ± 1.24
Entrapment efficiency (%)	92.84 ± 0.72	92.36 ± 0.76	92.08 ± 0.81	91.76 ± 0.84
Drug content (%)	98.24 ± 0.68	98.06 ± 0.72	97.78 ± 0.75	97.42 ± 0.79

Values are expressed as mean ± SD (n = 3).

The slight increase in particle size and PDI during storage may be associated with limited particle aggregation or rearrangement of the lipid matrix. However, the changes were relatively small and were not accompanied by significant loss of drug. The zeta potential remained sufficiently stable, while entrapment efficiency and drug content showed only minor reductions. Overall, the optimized F5 formulation demonstrated acceptable physical and chemical stability over the investigated storage period, supporting its suitability for further development as a telmisartan-loaded oral NLC system.

CONCLUSION:

The present study successfully demonstrated the formulation, optimization, and evaluation of telmisartan-loaded nanostructured lipid carriers (NLCs) as a potential approach for improving oral drug delivery. The pre-formulation investigation confirmed the characteristic properties of telmisartan and its poor aqueous solubility, supporting the need for a lipid-based delivery system. FTIR analysis indicated the compatibility of telmisartan with the selected formulation components without evidence of major chemical interactions.

NLC formulations were successfully prepared using a hot emulsification–ultrasonication technique with Compritol® 888 ATO as the solid lipid, a liquid lipid, and Poloxamer 188 as the surfactant. The formulations demonstrated nanoscale particle sizes ranging from 128.6 ± 3.21 to 198.4 ± 4.16 nm, with PDI values of 0.186 ± 0.012 to 0.312 ± 0.018, indicating formation of relatively homogeneous nanocarriers. The negative zeta potential values (−18.6 to −29.8 mV) suggested satisfactory surface charge characteristics and potential colloidal stability.

The entrapment efficiency of the formulations ranged from 78.42 ± 1.26% to 94.68 ± 0.84%, while drug loading varied from 5.18 ± 0.21% to 6.94 ± 0.18%. Increasing lipid concentration generally enhanced drug incorporation into the lipid matrix. Among the developed formulations, F5 provided a favorable overall balance of particle size, PDI, zeta potential, entrapment efficiency, drug loading, and drug-release characteristics. The optimized F5 formulation exhibited a particle size of 145.7 ± 2.84 nm, PDI of 0.214 ± 0.011, zeta potential of −25.6 ± 1.18 mV, entrapment efficiency of 92.84 ± 0.72%, and drug loading of 6.42 ± 0.16%.

The *in vitro* release study demonstrated that the NLC formulations provided prolonged release of telmisartan up to 12 h. Formulation F5 released 93.84% of the drug at 12 h, indicating effective control of drug release by the lipid matrix. The sustained-release behavior can be attributed to the incorporation of telmisartan within the lipid matrix, which can reduce direct drug diffusion and promote gradual release through diffusion and lipid-matrix erosion mechanisms.

Overall, the study indicates that telmisartan-loaded NLCs are a promising nanocarrier system for improving the physicochemical and release characteristics of telmisartan. The optimized formulation exhibited favorable nanoscale characteristics, high entrapment efficiency, and sustained drug release, suggesting its potential for enhanced oral delivery. Further investigations involving pharmacokinetic, in vivo bioavailability, and long-term stability studies are warranted to establish the therapeutic advantages of the optimized NLC formulation.

CONFLICT OF INTEREST:

The authors declare that there is no conflict of interest.

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