RESEARCH PAPER

Lipid-Based Microemulsion Approach for Oral Delivery of Atorvastatin Calcium Trihydrate: In Vitro Characterisation and Performance Evaluation

Harshini. KV*[1], Ezhilrasi.M[2], Geetha.V[3], Divya.K[4], Dr.T. Ayyappan[5]

[1]Department of Pharmaceutics Karpaga Vinayaga Institute for Pharmaceutical Sciences Karpaga Vinayaga Educational Lore for Learning (Deemed-to-be University) GST Road, Chinna Kolambakkam – 603308, Chengalpattu (Dt.), Tamil Nadu, India ORCID ID: 0009-0001-4519

[2]Department of Pharmacology Karpaga Vinayaga Institute for Pharmaceutical Sciences Karpaga Vinayaga Educational Lore for Learning (Deemed-to-be University) GST Road, Chinna Kolambakkam – 603308, Chengalpattu (Dt.), Tamil Nadu, India ORCID ID: 0009-0002-8411-8390

[3]Department of Pharmaceutical Analysis Karpaga Vinayaga Institute for Pharmaceutical Sciences Karpaga Vinayaga Educational Lore for Learning (Deemed-to-be University) GST Road, Chinna Kolambakkam – 603308, Chengalpattu (Dt.), Tamil Nadu, India ORCID ID: 0009-0007-0258-3771

[4]Department of Pharmaceutics Karpaga Vinayaga Institute for Pharmaceutical Sciences Karpaga Vinayaga Educational Lore for Learning (Deemed-to-be University) GST Road, Chinna Kolambakkam – 603308, Chengalpattu (Dt.), Tamil Nadu, India ORCID ID: 0009-0008-8058-8006

[5]Department of Pharmaceutics Karpaga Vinayaga Institute for Pharmaceutical Sciences Karpaga Vinayaga Educational Lore for Learning (Deemed-to-be University) GST Road, Chinna Kolambakkam – 603308, Chengalpattu (Dt.), Tamil Nadu, India ORCID ID: 0000-0002-7697-4608

***Corresponding Author:* Harshini. KV**
E-Mail: harshinivimala26@gmail.com
Received: 20th Jul, 2026; Revised: 27th Aug, 2026; Accepted: 22nd Oct, 2026

Abstract:
Atorvastatin calcium trihydrate is a lipid-lowering drug of Biopharmaceutics Classification System class II whose oral bioavailability is limited by poor aqueous solubility and extensive first-pass metabolism. This study aimed to develop and evaluate an oil-in-water microemulsion to improve its solubilisation and in vitro release. Methods: Seven formulations (F1 to F7) were prepared by the phase titration method using oleic acid as the oil phase, polysorbate 80 as surfactant, ethanol as co-surfactant and phosphate buffer pH 6.8 as the aqueous phase. Drug-excipient compatibility was examined by physical observation and Fourier transform infrared spectroscopy. The formulations were assessed for appearance, clarity, phase separation, pH, droplet size, zeta potential, viscosity, drug content, thermodynamic stability and in vitro release using Franz diffusion cells for 6 h. Results: The drug and excipients were compatible. Five formulations were clear and free of phase separation, whereas F4 and F7 were opaque and separated. The pH ranged from 5.85 to 6.25 and the viscosity from 0.887 to 0.905 cP. The optimised formulation F6 showed a drug content of 96.44%, a mean droplet size of 28.18 nm with a polydispersity index of 0.236, a zeta potential of -19.1 mV and a cumulative release of 90.5% at 6 h, compared with 73.2% to 88.0% for the other formulations. Release followed the Korsmeyer-Peppas model best ($R^2 = 0.998$). Conclusion: The oleic acid-polysorbate 80-ethanol microemulsion F6 is a promising oral carrier for atorvastatin; pure-drug comparison, long-term stability and in vivo studies are warranted.

Keywords: atorvastatin calcium trihydrate, microemulsion, oleic acid, polysorbate 80, phase titration, oral bioavailability, in vitro release

How to cite this article: Harshini. KV*1 Ezhilrasi.M2 Geetha.V. Lipid-Based Microemulsion Approach for Oral Delivery of Atorvastatin Calcium Trihydrate: In Vitro Characterisation and Performance Evaluation

Harshini. KV*1, Ezhilrasi.M2, Geetha.V[3], Divya.K4, Dr.T. Ayyappan5. Int J Drug Deliv Technol. 2026;16(87s):1689-1693. DOI: 10.25258/ijddt.16.87s.180.

1. Introduction

Hyperlipidaemia, characterised by raised blood cholesterol and triglycerides, promotes atherosclerosis and is a major contributor to coronary artery disease, myocardial infarction and stroke. Atorvastatin competitively inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of cholesterol biosynthesis, and thereby lowers low-density lipoprotein cholesterol and triglycerides. Despite this potent action, atorvastatin calcium belongs to Biopharmaceutics Classification System (BCS) class II: it is practically insoluble in water at neutral pH, and its oral bioavailability is only about 14% because of poor dissolution and extensive hepatic first-pass metabolism by cytochrome P450 3A4.[1,2]

Microemulsions are clear, isotropic and thermodynamically stable dispersions of oil and water stabilised by a surfactant and usually a co-surfactant, with

droplet sizes typically between 10 and 100 nm.[3,4] They solubilise lipophilic drugs in the oil phase or interfacial film, form with low energy input, are readily scaled up, and may protect the drug from hydrolysis and oxidation.[5,6,7] Microemulsions and related self-emulsifying systems have improved the oral performance of several poorly soluble drugs, including glimepiride, docetaxel, acyclovir, clopidogrel, amphotericin B and all-trans retinoic acid.[8,9,10,11,12,13]

For atorvastatin, self-emulsifying systems, microemulsions and microemulsion-based tablets have been reported to increase solubility and dissolution.[1,2,14,15,16,17,18] The present work therefore aimed to formulate an oral microemulsion of atorvastatin calcium trihydrate using oleic acid, polysorbate 80 and ethanol, and to characterise its physicochemical properties, stability and in vitro release in order to select an optimised composition.

2. Materials and Methods

2.1 Materials

Atorvastatin calcium trihydrate was obtained from Dhamtec Pharma and Consultants, Mumbai, India. Oleic acid, polysorbate 80 (Tween 80) and ethanol were purchased from Loba Chemie Pvt. Ltd., Mumbai, India. Phosphate buffer pH 6.8 was prepared in the laboratory. Instruments were a Shimadzu UV-1800 UV-visible spectrophotometer, a Shimadzu Fourier transform infrared (FT-IR) spectrophotometer, a Malvern particle size and zeta potential analyser, a Brookfield viscometer (Ametek), a digital pH meter (Infra Digi) and a capillary melting point apparatus (Guna Enterprises, Chennai).

2.2 Preformulation studies

Colour and odour were recorded descriptively. The pH was measured for 0.1 g of drug dispersed in 50 mL of distilled water. The melting point was determined in triplicate by the capillary method. Solubility was assessed in methanol, ethanol, phosphate buffer pH 6.8 and water. The wavelength of maximum absorption (λmax) was determined by scanning a 10 µg/mL methanolic solution between 200 and 400 nm. For the calibration curve, a stock solution (1 mg/mL) in phosphate buffer pH 6.8 was diluted to 2, 4, 6, 8 and 10 µg/mL and absorbance was read at λmax against buffer as blank.

2.3 Drug-excipient compatibility

Physical mixtures of the drug with oleic acid, polysorbate 80 and their combinations (including polysorbate 80 with ethanol) were stored at room temperature and at 40 ± 2 °C and 75 ± 5% relative humidity, and inspected after 10, 20 and 30 days. FT-IR spectra of the pure drug and of the drug with polysorbate 80 were recorded by the potassium bromide dispersion method.

2.4 Preparation of microemulsions

Microemulsions were prepared by the phase titration method. Atorvastatin calcium trihydrate (0.1 g) was dispersed in oleic acid with gentle stirring. Polysorbate 80 (surfactant) and ethanol (co-surfactant) were mixed to a clear, homogeneous surfactant mixture. The drug-loaded oil was added slowly to this mixture under constant stirring for 5 to 10 min. Phosphate buffer pH 6.8 was then added dropwise at room temperature with continuous stirring until a transparent or slightly bluish system formed, followed by a further 10 to 15 min of stirring. Seven formulations (F1 to F7) with different oil, surfactant, co-surfactant and aqueous phase contents were prepared **(Table 1).**

Table 1. Composition of atorvastatin calcium trihydrate microemulsions

Ingredient	F1	F2	F3	F4	F5	F6	F7
Oleic acid (mL)	1.0	1.2	1.5	1.0	1.3	1.0	1.6
Polysorbate 80 (mL)	4.0	3.5	3.0	5.0	4.5	3.2	2.5
Ethanol (mL)	1.5	1.8	1.5	1.0	1.2	2.0	1.4
Buffer pH 6.8 (mL)	3.5	3.5	3.5	3.0	3.0	3.8	4.5
Drug (g)	0.1	0.1	0.1	0.1	0.1	0.1	0.1

2.5 Evaluation of microemulsions

Appearance, homogeneity and clarity were examined against white and black backgrounds. Phase separation was checked after 24 h in transparent vials at room temperature. The pH was measured at 25 ± 1 °C. Droplet size and polydispersity index (PDI) were determined by dynamic light scattering and zeta potential and conductivity by electrophoretic light scattering (Malvern, 25 °C, water as dispersant). Viscosity was measured with the Brookfield viscometer. For drug content, an accurately measured sample was diluted with methanol to break the microemulsion and analysed by UV spectrophotometry at λmax. Thermodynamic stability was assessed by centrifugation (3000 rpm, 30 min) and six heating-cooling cycles between 4-8 °C and 40-45 °C; the freeze-thaw test was not performed because a freezing facility was unavailable.

2.6 In vitro release and kinetic analysis

In vitro release was studied in a Franz diffusion cell using phosphate buffer pH 6.8 (30 mL) at 37 ± 0.5 °C and 60 rpm for 6 h. Samples (1 mL) were withdrawn hourly and analysed by UV spectrophotometry. Release data of the optimised formulation were fitted to zero-order, first-order, Higuchi[19] and Korsmeyer-Peppas[20] models, and the coefficient of determination (R^2) was used to select the best-fit model.

2.7 Ethical statement

No human participants or animals were used; ethical committee approval was therefore not applicable.

3. Results and Discussion

3.1 Preformulation and compatibility

Atorvastatin calcium trihydrate was a white to off-white crystalline powder with a pH of 6.85 in aqueous dispersion. The melting point was 155, 156 and 157 °C (mean 156 °C), close to the reported 159-160 °C with decomposition. The drug was freely soluble in methanol (0.5 g in 5 mL), soluble in ethanol (0.5 g in 10 mL), sparingly soluble in phosphate buffer pH 6.8 (0.5 g in 20 mL) and very slightly soluble in water (0.5 g in 30 mL), confirming its poor aqueous solubility and the need for a solubilising carrier. The λmax was 242 nm, and the calibration curve was linear over 0 to 10 µg/mL ($y = 0.1097x - 0.0352$; $R^2 = 0.9952$).

No change in colour or physical state was observed for any drug-excipient combination at room temperature or at 40 °C/75% relative humidity for 30 days. The FT-IR spectrum of the drug showed the characteristic O-H/N-H stretching band at 3366.87 cm^{-1}, C=O stretching at 1701.66 cm^{-1}, C-C stretching at 1519.01 cm^{-1} and C-O

stretching at 1161.75 cm^{-1}. These principal bands were retained in the drug-polysorbate 80 mixture, indicating the absence of significant chemical interaction.

3.2 Physical appearance, pH, viscosity and drug content

All formulations were homogeneous, but their appearance depended on composition (Table 2). F1, F2 and F6 were transparent, F3 was slightly bluish and F5 was translucent, all clear without phase separation. F4 and F7 were milky and opaque and showed slight phase separation within 24 h, so they did not qualify as true microemulsions. The pH of all systems (5.85 to 6.25) was within the acceptable range for oral use, F6 being closest to neutral (6.25). All formulations had low viscosity (0.887 to 0.905 cP), close to water, indicating free-flowing systems suitable for oral administration and rapid dispersion in gastrointestinal fluids; F6 had the lowest value (0.887 cP).

Table 2. Physicochemical characteristics of formulations F1-F7

Code	pH	Appearance	Clarity	Phases paratin	Viscosity (cP)	Drug content (%)
F1	6.10	Transparent	Clear	No	0.905	86.08
F2	6.15	Transparent	Clear	No	0.895	80.25
F3	6.20	Slightly bluish	Clear	No	0.900	90.93
F4	5.85	Milky	Opaque	Yes	0.892	82.84
F5	6.05	Translucent	Clear	No	0.898	88.18
F6	6.25	Transparent	Clear	No	0.887	96.44
F7	5.90	Milky	Opaque	Yes	0.899	78.64

Drug content ranged from 78.64% to 96.44%. Only F6 (96.44%) fell within the 95-105% range generally expected for liquid dosage forms, whereas the others (78.6 to 90.9%) probably reflect incomplete solubilisation or loss during preparation. The higher content of F6 coincided with the largest co-surfactant fraction (2.0 mL ethanol) and a moderate surfactant level.

3.3 Droplet size, zeta potential and stability

The optimised formulation (F6) had a Z-average droplet size of 28.18 nm and a PDI of 0.236, within the microemulsion range of 10 to 100 nm and below the 0.3 limit for a narrow distribution. The intensity distribution was, however, multimodal: peaks at 2.86 nm (58.3%), 47.09 nm (36.1%) and 5356 nm (5.6%). The smallest population may represent surfactant micelles, and the largest minor population probably reflects a few aggregates or dust, so these data should be confirmed with repeated measurements and volume-weighted distributions. The mean size is smaller than the 57.61 nm reported for another atorvastatin microemulsion.[2] The size distribution is shown in **Figure 1.**

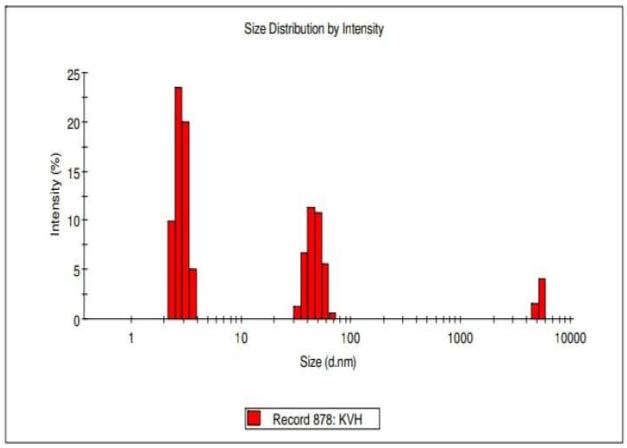


Figure 1. Particle size distribution by intensity of the optimised microemulsion F6 (Malvern, 25 °C; Z-average 28.18 nm, PDI 0.236).

The zeta potential was -19.1 mV (SD 13.0 mV), with two populations at -11.1 mV (58.2%) and -31.0 mV (41.8%) and a conductivity of 0.617 mS/cm. The high conductivity supports an oil-in-water structure with a continuous aqueous phase. Because polysorbate 80 is non-ionic, stability is expected to depend mainly on steric rather than electrostatic repulsion, so the moderate negative charge (Figure 2) is acceptable but indicates only moderate electrostatic stabilisation. All seven formulations showed no phase separation, creaming, turbidity or precipitation after centrifugation or heating-cooling cycles; freeze-thaw and long-term storage stability remain to be evaluated.

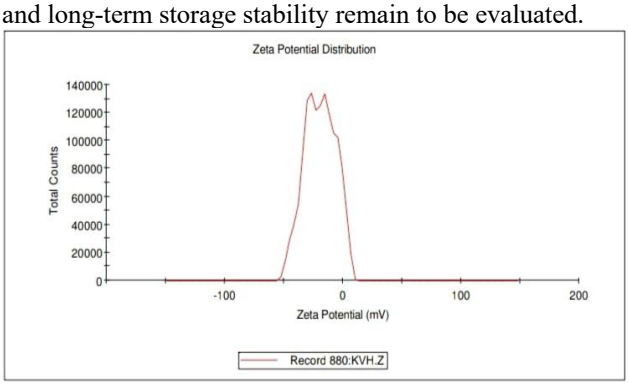


Figure 2. Zeta potential distribution of the optimised microemulsion F6 (mean -19.1 mV).

3.4 In vitro drug release

Cumulative release after 6 h (Figure 3a) was 75.9, 82.4, 79.5, 88.0, 73.2, 90.5 and 81.6% for F1 to F7, respectively. F6 released the most drug at every sampling time (16.5% at 1 h and 90.5% at 6 h). F4 also released rapidly (88.0%) but was physically unstable, and F7 showed an irregular profile (sudden rise between 4 and 5 h), consistent with its phase separation. The faster release of F6 is consistent with its lower viscosity, small droplet size and higher co-surfactant content, which favour drug partitioning from the oil droplets into the aqueous medium. The study did not include a pure-drug control, so the improvement relative to unformulated atorvastatin could not be quantified here; earlier self-emulsifying systems of atorvastatin showed several-fold higher dissolution than pure drug,[16,17] although differences in apparatus preclude direct comparison.

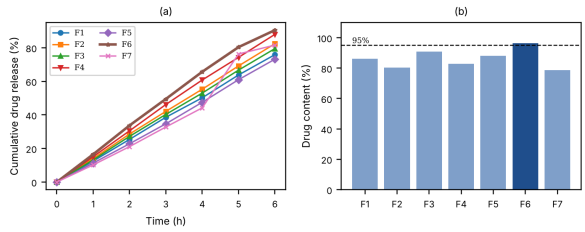


Figure 3. (a) Cumulative in vitro release of atorvastatin calcium trihydrate from formulations F1-F7 in phosphate buffer pH 6.8 and (b) drug content of the formulations.

Kinetic modelling of the F6 release data gave R^2 values of 0.9944 (zero order), 0.9522 (first order), 0.9945 (Higuchi) and 0.9979 (Korsmeyer-Peppas) (Table 3). The Korsmeyer-Peppas model fitted best, with a release exponent (n) of 0.96. A value of n close to 1 indicates release that is nearly linear with time, which suggests a relaxation- or partition-controlled process at the droplet-medium interface rather than purely Fickian diffusion; the proposed mechanism should be verified with additional time points and a pure-drug reference.

Table 3. Release kinetics of the optimised formulation F6

Model	Equation of fitted line	R^2
Zero order	y = 15.04x + 3.42	0.9944
First order	y = -0.185x + 2.190	0.9522
Higuchi	y = 52.33x - 38.42	0.9945
Korsmeyer-Peppas	y = 0.961x + 1.229 (n = 0.96)	0.9979
Model	**Equation of fitted line**	**R^2**
Zero order	y = 15.04x + 3.42	0.9944
First order	y = -0.185x + 2.190	0.9522
Higuchi	y = 52.33x - 38.42	0.9945
Korsmeyer-Peppas	y = 0.961x + 1.229 (n = 0.96)	0.9979

3.5 Limitations

This is a laboratory-scale study of seven compositions with a single optimised batch characterised in detail. Pseudo-ternary phase diagrams, a pure-drug control, freeze-thaw and long-term storage studies and in vivo pharmacokinetics were not included and should be addressed before clinical inference.

4. Conclusion

An oral oil-in-water microemulsion of atorvastatin calcium trihydrate was successfully prepared from oleic acid, polysorbate 80, ethanol and phosphate buffer pH 6.8. The drug was compatible with the excipients. Formulation

F6 was selected as optimal on the basis of clarity, absence of phase separation, near-neutral pH, lowest viscosity, drug content of 96.44%, droplet size of 28.18 nm and the highest in vitro release (90.5% at 6 h), with release best described by the Korsmeyer-Peppas model. F6 is a promising carrier for improving the oral delivery of atorvastatin, and further work on pure-drug comparison, stability and in vivo bioavailability is recommended.

References

1. Kadu PJ, Kushare SS, Thacker DD, Gattani SG. Enhancement of oral bioavailability of atorvastatin calcium by self-emulsifying drug delivery systems (SEDDS). Pharm Dev Technol. 2011;16:65-74
2. Rana H, et al. Development of microemulsion for solubility enhancement of atorvastatin calcium. Int J Pharm Sci Res. 2013;4(10):3103-9
3. Danielsson I, Lindman B. The definition of microemulsion. Colloids Surf. 1981;3:391-2.
4. Hellweg T. Phase structure of microemulsions. Curr Opin Colloid Interface Sci. 2002;7:50-6.
5. Tenjarla S. Microemulsions: an overview and pharmaceutical applications. Crit Rev Ther Drug Carrier Syst. 1999;16:461-521.
6. Narang AS, Delmarre D, Gao D. Stable drug encapsulation in micelles and microemulsions. Int J Pharm. 2007;345:9-25.
7. Sanap D, Ghugu P. Microemulsion as a potential carrier for improved drug delivery. J Res Pharm. 2024;28(6):2202-14.
8. Shen S, Li H, et al. Improved oral bioavailability of poorly water soluble glimepiride by utilizing microemulsion technique. Int J Nanomedicine. 2016;11:3777-88
9. Yin YM, Cui FD, Mu CF, et al. Docetaxel microemulsion for enhanced oral bioavailability: preparation and in vitro and in vivo evaluation. J Control Release. 2009;140(2):86-94.
10. Ghosh PK, Majithiya RJ, Umrethia ML, Murthy RSR. Design and development of microemulsion drug delivery system of acyclovir for improvement of oral bioavailability. AAPS PharmSciTech. 2006;7(3):E77.
11. Patel V, Kukadiya H, Mashru R, Surti N, Mandal S. Development of microemulsion for solubility enhancement of clopidogrel. Iran J Pharm Res. 2010;9(4):327-34.
12. Silva AE, Barratt G, Chéron M, Egito EST. Development of oil-in-water microemulsions for the oral delivery of amphotericin B. Int J Pharm. 2013;454(2):641-8.
13. Subongkot T, Ngawhirunpat T. Development of a novel microemulsion for oral absorption enhancement of all-trans retinoic acid. Int J Nanomedicine. 2017;12:5585-99.
14. Patel NK, Panara J. Formulation and development of microemulsion based tablets of atorvastatin calcium. J Pharm Sci Bioscientific Res. 2015;5(5):457-62.
15. Czajkowska-Kosnik A, Szekalska M, Winnicka K. Development and evaluation of liquid and solid self-emulsifying drug delivery systems for atorvastatin. Molecules. 2015;20:21010-22.
16. Khan F, Roni MA, Islam MS, et al. Systematic development of self-emulsifying drug delivery systems of atorvastatin with improved

bioavailability potential. Sci Pharm. 2012;80:1027-43.

17. Bhise K, Bora D. Formulation and evaluation of self microemulsion drug delivery system of low solubility drug for enhanced solubility and dissolution. Asian J Biomed Pharm Sci. 2014;4(22):622.
18. Mandal S, Mandal SS, Sawant KK. Design and development of microemulsion drug delivery system of atorvastatin and study its intestinal permeability in rats. Int J Drug Deliv. 2010;2(1).
19. Higuchi T. Mechanism of sustained-action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963;52:1145-9.
20. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15:25-35.