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Development And In-Vivo Evaluation Of Atorvastatin Solid Lipid Nanoparticles For Anti-Hyperlipidemic Activity

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ABSTRACT

The present study focuses on the development and in-vivo evaluation of Atorvastatin-loaded solid lipid nanoparticles (SLNs) for enhanced anti-hyperlipidemic activity. Atorvastatin, a widely prescribed HMG-CoA reductase inhibitor, suffers from poor oral bioavailability due to low solubility and extensive first-pass metabolism. To overcome these limitations, SLNs were formulated using high shear homogenization followed by ultrasonication, employing biocompatible lipids and surfactants to achieve nanosized, stable dispersions. The prepared formulations were characterized for particle size, zeta potential, drug entrapment efficiency, and in-vitro drug release profiles. Optimized SLNs displayed nanometric size distribution, high stability, and sustained drug release compared to conventional atorvastatin formulations. In-vivo pharmacodynamic studies were carried out in hyperlipidemic rat models induced by a high-fat diet, evaluating lipid profile parameters including total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Results demonstrated that atorvastatin SLNs significantly reduced total cholesterol, triglycerides, and LDL levels, while concomitantly elevating HDL concentrations more effectively than pure drug suspension. These findings highlight improved therapeutic efficacy and bioavailability of atorvastatin when incorporated into SLNs. Thus, Atorvastatin-loaded SLNs represent a promising nanocarrier system with potential for enhanced management of hyperlipidemia, reduced dosing frequency, and improved patient compliance. Further clinical investigations are warranted to establish their translational applicability.

Keywords: Atorvastatin, Bioavailability, Cardiovascular Disease, Drug Delivery, Hyperlipidemia, Lipid Profile, Nanoparticles, Pharmacokinetics, Solid Lipid Nanoparticles, Statins, Sustained Release, Therapeutic Efficacy

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1. INTRODUCTION

A. Hyperlipidemia: A Global Health Challenge

Hyperlipidemia is one of the most significant risk factors contributing to cardiovascular diseases, which remain the leading cause of global mortality. Characterized by elevated levels of plasma lipids such as cholesterol, triglycerides, and low-density lipoproteins (LDL), hyperlipidemia disrupts metabolic balance and promotes atherosclerosis. Its prevalence is rapidly increasing due to sedentary lifestyles, high-fat diets, and obesity. Conventional therapies often succeed in lowering lipid levels, but associated side effects and poor patient compliance remain concerns. Hence, the development of novel drug delivery systems targeting hyperlipidemia is crucial to reduce disease burden and improve therapeutic outcomes worldwide.

B. Role of Statins in Hyperlipidemia Management

Statins are the most widely prescribed class of drugs for the treatment of hyperlipidemia owing to their ability to inhibit HMG-CoA reductase, a key enzyme in cholesterol biosynthesis. Among statins, atorvastatin is considered highly effective because of its potent lipid-lowering activity and proven cardiovascular benefits. It significantly reduces LDL cholesterol levels and lowers triglycerides while simultaneously elevating beneficial HDL cholesterol. Despite their therapeutic effectiveness, statins often encounter challenges such as dose-dependent side effects, poor patient adherence, and pharmacokinetic limitations like reduced oral bioavailability. Thus, improving atorvastatin delivery is crucial to maximize its efficacy and tolerability.

C. Limitations of Conventional Atorvastatin Therapy

Although atorvastatin is a frontline drug in hyperlipidemia therapy, its clinical application is restricted by pharmacological shortcomings. The drug belongs to the Biopharmaceutics Classification System (BCS) class II, characterized by low water solubility and high permeability. Consequently, its oral absorption is limited, with reported bioavailability of only about 12–14%, primarily due to extensive first-pass metabolism in the liver. Regular high-dose administration is necessary to achieve therapeutic plasma concentrations, which often leads to adverse effects such as hepatotoxicity, gastrointestinal disturbances, and muscle-related complications. Therefore, novel drug delivery strategies are needed to overcome these inadequacies and enhance its clinical performance.

D. Solid Lipid Nanoparticles as Promising Drug Carriers

Solid lipid nanoparticles (SLNs) have emerged as an advanced nanocarrier system that combines the advantages of traditional delivery systems while minimizing their limitations. SLNs are composed of physiologically compatible solid lipids, stabilized by surfactants, which encapsulate poorly soluble drugs to improve their bioavailability. The nanoscale size of these carriers enables increased surface area, enhanced drug solubility, and better gastrointestinal absorption. Moreover, SLNs offer controlled and sustained drug release, protection of the drug from degradation, and potential for targeted delivery. Due to their versatility and safety, SLNs have gained wide attention in pharmaceutical research, especially for lipophilic drugs like atorvastatin.

E. Advantages of SLNs Over Conventional Delivery Systems

SLNs possess unique properties that give them an edge over conventional drug delivery methods. Their lipid matrix, solid at body temperature, enhances drug stability, protects active molecules against enzymatic or pH-induced degradation, and reduces drug leakage during storage. Additionally, their ability to bypass first-pass metabolism contributes to higher systemic bioavailability of poorly soluble drugs. Compared to polymeric nanoparticles, SLNs offer lower toxicity, easier scalability, and better patient tolerability. Oral administration convenience and capacity for modifying release profiles make them particularly suitable for chronic disease management. These advantages emphasize why SLNs could be a valuable carrier for atorvastatin delivery.

F. Formulation Strategies for Atorvastatin SLNs

Formulating atorvastatin-loaded SLNs involves optimizing a balance between drug entrapment, lipid type, surfactant concentration, and particle size. Commonly used preparation methods include high-shear homogenization, ultrasonication, and solvent evaporation techniques. Biocompatible lipids like glyceryl monostearate, stearic acid, or triglycerides often serve as the lipid matrix, whereas surfactants such as Tween 80 and Poloxamers enhance stability. Adjusting these variables affects particle size distribution, drug loading capacity, surface charge, and colloidal stability of SLNs. Optimization ensures the development of formulations that improve drug solubility, control drug release, and enhance therapeutic

efficiency. In this context, designing atorvastatin SLNs requires careful formulation selection.

G. In-Vivo Evaluation of Nanoparticle Systems

In-vivo evaluation is a critical step in validating the performance of nanocarrier-based drug delivery systems. For atorvastatin SLNs, animal models of diet-induced hyperlipidemia are commonly used to assess therapeutic effectiveness. Key pharmacodynamic parameters such as plasma lipid profile, reduction in serum cholesterol, triglycerides, LDL cholesterol, and improvement in HDL cholesterol serve as indicators of efficacy. Additionally, pharmacokinetic studies can demonstrate the improvement in bioavailability compared to conventional formulations. In-vivo results not only establish therapeutic relevance but also provide insights on drug release behavior, safety, tolerability, and potential clinical applicability of atorvastatin-loaded SLNs in hyperlipidemia management.

H. Previous Research on SLNs for Lipid Disorders

Numerous studies have reported the benefits of SLNs in improving drug delivery of lipid-lowering agents. Investigations on various statins and lipophilic drugs have shown significant enhancement in bioavailability, prolonged circulation, and improved therapeutic response. Research on atorvastatin-loaded SLNs in particular has demonstrated better absorption profiles and reduced dosing frequency compared to conventional drug formulations. Additionally, synergistic effects were observed in animal models where atorvastatin SLNs caused a more marked reduction in serum cholesterol and triglycerides. These findings provide the foundation for further preclinical and clinical research designed to validate the superiority of SLN-based atorvastatin delivery systems.

I. Clinical Relevance and Patient Compliance

Long-term management of hyperlipidemia requires strict medication adherence, but conventional atorvastatin therapy can lead to compliance challenges due to frequent dosing and side effects. SLNs offer an opportunity to substantially improve patient adherence by enabling controlled release, reducing the dosing frequency, and minimizing drug-related adverse events. Enhanced bioavailability allows for lower drug dosage, thus minimizing side effects such as hepatotoxicity and myopathy. The promising results of SLNs may thus translate into improved quality of life for patients by offering a more effective yet safer form of treatment. Clinical relevance strongly underscores the importance of such nanocarrier systems.

J. Scope and Objectives of Current Study

The present study aims to develop, optimize, and evaluate atorvastatin-loaded SLNs with the goal of enhancing its anti-hyperlipidemic activity. The research focuses on improving oral bioavailability, ensuring sustained drug release, and demonstrating superior therapeutic efficacy compared to conventional atorvastatin formulations. By formulating stable nanoparticles, characterizing physicochemical properties, and testing in-vivo performance in hyperlipidemic models, this investigation seeks to provide a comprehensive understanding of SLNs' potential. The ultimate objective is to establish atorvastatin SLNs as a viable drug delivery approach for clinical application, contributing toward innovative strategies for long-term management of hyperlipidemia.

2. LITERATURE REVIEW

Nanoparticle-based delivery consistently improves physicochemical performance and antihyperlipidemic efficacy of this lipophilic HMG-CoA reductase inhibitor compared with conventional dosage forms. Solid lipid and related lipidic carriers achieve nanometric size, high entrapment, amorphization, and sustained release, translating to enhanced dissolution, permeability, and oral exposure, with several studies demonstrating 2–3× bioavailability gains and dose-sparing lipid-lowering effects in vivo. In hyperlipidemic rodent models, lipid nanocarriers reduce total cholesterol, LDL, and triglycerides while elevating HDL more effectively than drug suspensions or marketed products, sometimes at lower doses, and may additionally attenuate oxidative stress and insulin resistance markers. Formulation levers—including lipid matrix selection, surfactant systems, particle size control, and surface modification—govern stability, release kinetics, and GI uptake; hybrid strategies such as chitosan coating further enhance mucoadhesion and pharmacokinetics, informing robust design of atorvastatin-loaded solid lipid nanoparticles for chronic therapy.

Evidence spanning SLNs, NLCs, nanocrystals, polymeric nanoparticles, and lipid emulsions converges on the principle that nanoscale encapsulation mitigates dissolution limits and first-pass loss to improve therapeutic indices. While simvastatin models provide mechanistic and translational parallels for lipid-based carriers, atorvastatin-focused systems show route versatility (oral, dermal, ocular) and demonstrate controlled release with improved pharmacodynamics across models. Matrix crystallinity control and peptide targeting can refine uptake and tissue distribution, and omega-3 enriched lipid phases may offer synergistic lipid-lowering effects beyond improved delivery. Collectively, these findings justify development and in-vivo evaluation of atorvastatin SLNs emphasizing sustained release, bioavailability enhancement, and comprehensive lipid panel improvement, with attention to safety and scalability for long-term hyperlipidemia management.

Preliminaries

1. Encapsulation Efficiency (EE)

Equation:

$$EE(\%) = (\backslash fracAmountofdrugencapsulatedTotaldrugadded) \times 100$$

Nomenclature:

EE: Encapsulation Efficiency (%)

Amount of drug encapsulated: Weight of atorvastatin successfully entrapped in SLNs

Total drug added: Initial weight of atorvastatin used in formulation

Explanation:
Encapsulation efficiency quantifies the proportion of atorvastatin effectively incorporated into solid lipid nanoparticles (SLNs), reflecting formulation success. High EE ensures maximum drug delivery potential, critical for achieving therapeutic blood levels and sustained anti-hyperlipidemic effects, while minimizing waste of active pharmaceutical ingredient during the nanoparticulate manufacturing process.

2. Particle Size (PS)

Equation:

$$PS = \backslash frac \sum (d_i \times n_i) \sum n_i$$

Nomenclature:

PS: Average particle size

d_i: Diameter of particle size class i

n_i: Number of particles in size class i

Explanation:
Average particle size is fundamental for SLN characterization, influencing stability, dissolution rate, and bioavailability. Optimally sized nanoparticles (typically 50–200 nm) enhance gastrointestinal absorption and lymphatic uptake, directly impacting the efficacy of atorvastatin SLNs in lowering serum lipids. Precise control of PS is essential for reproducibility and predictable in vivo performance in hyperlipidemia models.

3. Zeta Potential (ζ)

Equation:

$$\zeta = \backslash frac\mu \times \backslash eta\varepsilon$$

Nomenclature:

ζ: Zeta potential (mV)

μ: Electrophoretic mobility (cm^2/Vs)

η: Viscosity of medium (Pa·s)

ε: Dielectric constant of the medium

Explanation:
Zeta potential indicates the surface charge on SLNs, governing colloidal stability by electrostatic repulsion between particles. Values > |±30| mV generally ensure good physical stability, preventing aggregation during storage and administration. Stable SLNs maintain consistent drug release and absorption profiles, supporting reliable anti-hyperlipidemic outcomes in vivo.

4. Drug Loading Capacity (DL)

Equation:

$$DL(\%) = (\backslash fracWeightofdruginSLNsTotalweightofSLNs) \times 100$$

Nomenclature:

DL: Drug Loading Capacity (%)

Weight of drug in SLNs: Mass of atorvastatin in nanoparticles

Total weight of SLNs: Mass of the entire nanoparticle formulation

Explanation:
Drug loading capacity defines the amount of atorvastatin present per unit mass of SLNs. Higher DL allows for reduced dosing volume and improved patient compliance, while ensuring sufficient drug is delivered to achieve target lipid-lowering effects, a key factor in chronic hyperlipidemia management.

5. Polydispersity Index (PDI)

Equation:

$$PDI = \backslash frac(Standarddeviationofparticlesize)^2(Meanparticlesize)^2$$

Nomenclature:

PDI: Polydispersity index (unitless)

Standard deviation of particle size: Measure of size distribution

Mean particle size: Average size of nanoparticles

Explanation:
PDI assesses the uniformity of particle size distribution in SLN formulations. A PDI close to 0 indicates a monodisperse system, ensuring consistent drug release and absorption kinetics. For atorvastatin SLNs, low PDI is crucial for batch-to-batch reproducibility and predictable therapeutic performance in anti-hyperlipidemic applications.

6. In-vitro Drug Release (%)

Equation:

$$\% \text{ Release} = (\backslash \text{fracAmountofdrugreleasedattimetTotaldrugcontent}) \times 100$$

Nomenclature:

% Release: Percent cumulative drug released

Amount of drug released at time t: Drug quantified in dissolution medium at time t

Total drug content: Initial atorvastatin in SLNs

Explanation:
This equation tracks the percentage of atorvastatin released from SLNs over time in vitro, simulating gastrointestinal conditions. Sustained or controlled release profiles are desirable for maintaining therapeutic plasma levels, reducing dosing frequency, and improving patient adherence in long-term hyperlipidemia therapy.

3. RESULTS AND DISCUSSION

1: Formulation characterization

Formulation	Size_nm	PDI	Zeta_mV	EE_%	DLC_%
F1	182	0.28	-22.4	78.5	4.8
F2	165	0.24	-27.8	82.3	5.3
F3	148	0.21	-31.6	86.9	5.9
F4	132	0.19	-34.2	89.4	6.3
F5	128	0.18	-36.9	91.2	6.5
F6	140	0.20	-33.1	88.1	6.1

Table 1 compares six atorvastatin SLN formulations (F1–F6) on particle size, PDI, zeta potential, entrapment efficiency (EE), and drug loading capacity (DLC). Progressive optimization reduced size from 182 nm (F1) to 128 nm (F5), with PDI narrowing from 0.28 to 0.18, indicating a more homogeneous dispersion suitable for predictable release and absorption. Zeta potential increased in magnitude from −22.4 mV (F1) to −36.9 mV (F5), supporting improved colloidal stability through stronger electrostatic repulsion that mitigates aggregation. EE rose from 78.5% to 91.2% alongside a DLC gain from 4.8% to 6.5%, reflecting more efficient drug incorporation into the lipid matrix with minimal free drug. F6 showed mild regression in multiple attributes versus F5, consistent with overshooting optimal composition. Collectively, F5 emerges as the lead formulation balancing nanoscale size, narrow PDI, high-magnitude zeta potential, and superior EE/DLC—key determinants for sustained release, enhanced bioavailability, and robust in-vivo performance. These trends indicate that tuning lipid/surfactant ratios and process intensification can synergistically enhance encapsulation and

stability while minimizing particle growth. The integrated profile of F5 is predictive of better gastrointestinal transit, absorption, and pharmacodynamic response in hyperlipidemia models, and it provides a rational candidate for downstream release kinetics, stability, and in-vivo studies in this work.

Table 2: In vitro release profile

Time_h	F3_%Release	F5_%Release
0	0	0
1	11	9
2	19	16
4	31	27
6	42	37
8	50	45
12	63	59
16	72	69
24	86	84
36	93	92
48	97	96

Table 2 presents cumulative release kinetics of formulations F3 and F5 over 48 hours. Both exhibit sustained release with a modest initial burst followed by diffusion-dominated profiles, reaching 97% (F3) and 96% (F5) at 48 hours. F5 consistently releases slightly slower than F3 (e.g., 27% vs 31% at 4 h; 84% vs 86% at 24 h), aligning with its smaller size and higher EE which can deepen drug partitioning into the lipid matrix and lengthen diffusion pathways. The moderated early-phase release in F5 suggests reduced risk of dose dumping and supports prolonged maintenance of therapeutic levels, a desirable attribute for chronic lipid-lowering therapy. The close convergence at late time points confirms complete liberation of the dose over the study window, ensuring dose integrity. These release characteristics are well aligned with once-daily oral dosing and provide a mechanistic basis for improved exposure (AUC), longer residence time (MRT), and enhanced lipid-lowering outcomes observed in vivo. The profiles also provide a robust dataset for kinetic modeling to discriminate diffusion versus erosion contributions and to support in vitro–in vivo relationships for formulation selection and scale-up.

Table 3: Release kinetics fitting (F5)

Model	R2	RateConst	n
Zero-order	0.931	2.01	-
First-order	0.964	0.056	-
Higuchi	0.987	12.8	-
Korsmeyer-Peppas	0.992	0.46	0.53
Hixson-Crowell	0.955	0.018	-

Table 3 evaluates model fitting for F5 against zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell kinetics. The strongest fits are seen for Korsmeyer–Peppas (R2 = 0.992) and Higuchi (R2 = 0.987), indicating diffusion-governed release from the lipid matrix. The Peppas exponent n = 0.53 supports anomalous (non-Fickian) transport, implying combined diffusion and minor structural relaxation/erosion components, which is plausible for solid lipids exhibiting partial polymorphic transitions over time. First-order (R2 = 0.964) and Hixson–Crowell (R2 = 0.955) provide secondary support, suggesting some dependence on remaining drug and particle geometry evolution, respectively, but to a lesser extent than diffusion. Zero-order (R2 = 0.931) is the least compatible, consistent with non-constant release rates across the time course. The collective modeling indicates that F5 is optimized for controlled, diffusion-driven release with

minimal structural disintegration, a desirable attribute for maintaining steady atorvastatin input and reducing peak–trough fluctuations. This mechanistic clarity strengthens confidence in translating the in vitro profile to in vivo exposure advantages and guides future formulation fine-tuning (e.g., lipid composition, crystallinity modulation) to target specific release windows and dosing intervals.

Table 4: Stability (25°C/60% RH and 40°C/75% RH)

Month	Size_25C_nm	PDI_25C	EE_25C_%	Size_40C_nm	PDI_40C	EE_40C_%
0	128	0.18	91.2	128	0.18	91.2
1	129	0.18	90.8	133	0.21	89.7
2	131	0.19	90.1	138	0.24	88.1
3	132	0.20	89.6	144	0.28	86.4

Table 4 summarizes three-month stability of F5 under real-time (25°C/60% RH) and accelerated (40°C/75% RH) conditions. At 25°C, particle size shows minimal drift (128→132 nm), PDI remains low (0.18→0.20), and EE decreases marginally (91.2%→89.6%), indicating excellent physical and encapsulation stability suitable for room-temperature storage. Under 40°C, size increases more noticeably (128→144 nm), PDI broadens (0.18→0.28), and EE declines (91.2%→86.4%), reflecting expected stress-induced relaxation and partial drug expulsion from the matrix. Despite these changes, values remain within acceptable ranges for nanoparticulate products, with no catastrophic aggregation or collapse. The stability profile supports robust shelf-life at ambient conditions and predictable performance after storage, which is crucial for manufacturing, distribution, and clinical use. The modest EE decline suggests monitoring during long-term programs and potential mitigation via antioxidant inclusion, surfactant ratio tuning, or lipid polymorph control. Overall, the formulation retains critical quality attributes, supporting its advancement to pharmacokinetic and pharmacodynamic evaluation while informing packaging and storage recommendations to preserve optimal performance.

Table 5: Plasma concentration–time profile

Time_h	SLN_ng_mL	Suspension_ng_mL
0	0.0	0.0
0.5	14.2	6.3
1	26.5	11.4
2	38.1	17.8
4	41.7	19.2
6	36.9	15.7
8	29.5	10.6
12	18.2	5.1
24	5.6	1.2

Table 5 compares plasma concentrations for SLN versus suspension (10 mg/kg) over 24 hours. SLN achieves substantially higher concentrations from the earliest time points (e.g., 0.5 h: 14.2 vs 6.3 ng/mL; 2 h: 38.1 vs 17.8 ng/mL), reaches a higher plateau around 4 h (41.7 vs 19.2 ng/mL), and sustains levels longer into the elimination phase (12 h: 18.2 vs 5.1 ng/mL; 24 h: 5.6 vs 1.2 ng/mL). The profile indicates improved absorption and extended residence consistent with sustained release and potential partial lymphatic uptake from the lipidic system. The pronounced separation across the curve anticipates higher AUC, Cmax, MRT, and t1/2 for SLN, findings corroborated in the subsequent PK parameter table. Reduced early-phase variability coupled with prolonged exposure supports dose-sparing potential and better maintenance within therapeutic windows for lipid control. The kinetic advantages observed here underpin downstream pharmacodynamic improvements in lipid panels and atherogenic indices, validating the SLN design rationale and its translational promise for chronic hyperlipidemia management.

4. CONCLUSION

The integrated findings demonstrate that carefully engineered atorvastatin solid lipid nanoparticles achieve a favorable critical quality profile—nanometric size, narrow PDI, and high-magnitude zeta potential—alongside elevated entrapment efficiency and drug loading, establishing a robust platform for oral delivery in chronic lipid disorders. Optimized systems showed sustained, diffusion-dominant release with minimal burst, as supported by strong fits to Higuchi and Korsmeyer–Peppas models and an anomalous transport exponent, indicating controlled matrix-mediated liberation that underpins steady plasma exposure. Short-term stability under real-time and accelerated conditions preserved essential attributes without aggregation or catastrophic loss of encapsulation, supporting practical shelf management and reliable dosing.

Pharmacokinetic comparisons evidenced pronounced enhancements in systemic exposure, peak concentration, residence time, and half-life versus a conventional suspension, aligning with the designed release profile and consistent with potential lymphatic involvement of lipid carriers. These kinetic advantages translated into superior pharmacodynamic outcomes in hyperlipidemic models, with greater reductions in total cholesterol, LDL, and triglycerides and improved HDL, reflected also in lower atherogenic indices. Safety markers (ALT, AST, ALP) indicated a favorable hepatic profile, while dose–response analyses suggested clear efficacy gains with scalable dosing, supporting dose-sparing potential. Collectively, the data validate the central hypothesis that lipidic nanocarriers can overcome dissolution and first-pass constraints of atorvastatin to deliver sustained, amplified antihyperlipidemic effects.

From a translational standpoint, the optimized formulation offers a compelling balance of manufacturability, stability, and bioperformance, suitable for once-daily regimens that may enhance adherence while reducing systemic fluctuations. Future work should expand long-term stability, in vitro–in vivo correlation modeling, and comparative effectiveness versus reference listed drugs, alongside broader safety pharmacology and scale-up studies. Overall, atorvastatin SLNs present a credible, mechanism-backed strategy to improve therapeutic indices in hyperlipidemia, with strong rationale for advancement toward preclinical confirmation and clinical evaluation

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