Review

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Innovative Conjugation Strategies in Atherosclerosis: Charting New Pathways in Lipid-Lowering Therapies From a Pharmacological Perspective

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Abstract

Atherosclerosis, a leading cause of cardiovascular morbidity and mortality, is driven by lipid accumulation and inflammation within arterial walls. While statins have been pivotal in managing this condition by lowering low-density lipoprotein cholesterol, limitations such as statin intolerance and genetic variability highlight the need for innovative therapeutic strategies. Conjugation synthesis, which involves the chemical linkage of statins with polymers, nanoparticles, or bioactive molecules, represents a promising strategy to enhance the pharmacokinetics and pharmacodynamics of these agents. This approach improves drug solubility, stability, bioavailability, and targeted delivery, resulting in superior low-density lipoprotein cholesterol reduction, enhanced plaque stabilization, and reduced systemic side effects compared to traditional statins therapies. Studies have shown that polymer-based and nanotechnology conjugations not only optimize drug delivery but also minimize adverse effects, potentially transforming the treatment landscape of atherosclerosis. As research advances, these next-generation therapies have the potential to provide more personalized and effective treatment options for patients.

Keywords: Atherosclerosis; Statins; Conjugation strategies; Cardiovascular therapeutics; Targeted lipid reduction

1. Introduction

Atherosclerosis, a chronic inflammatory disease characterized by the buildup of plaques within arterial walls, remains a leading cause of cardiovascular morbidity and mortality worldwide. Despite significant advances in medical treatment, including the widespread use of statin therapy, the global burden of atherosclerosis continues to pose severe public health challenges. According to the World Health Organization, cardiovascular diseases, primarily driven by atherosclerosis, account for approximately 17.9 million deaths annually, making them the leading cause of death worldwide.[1–3] Given the persistent impact of atherosclerosis, there is a critical need for more effective prevention and treatment strategies. Statin therapy has long been the cornerstone of managing atherosclerosis due to its efficacy in lowering cholesterol levels, particularly low-density lipoprotein cholesterol (LDL-C), a major contributor to plaque formation.[4] Statins function by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase, an enzyme involved in the biosynthesis of cholesterol in the liver, thereby reducing LDL-C levels and slowing the progression of atherosclerosis.[5–7] Figure 1 illustrates the mechanism of action of statins in reducing cholesterol and plaque formation.

Traditional statins often face challenges such as poor solubility, rapid clearance from the bloodstream, and systemic side effects due to non-specific distribution necessitates the development of more advanced therapeutic approaches. This has led to the exploration of innovative strategies, such as conjugation synthesis, which aims to enhance the pharmacokinetics and pharmacodynamics of statins.[8,9] By linking statins with polymers, nanoparticles, or bioactive molecules, these next-generation therapies offer improved drug solubility, stability, bioavailability, and targeted delivery, potentially transforming the treatment landscape for atherosclerosis.[10,11] Figure 2 shows the chemical structures of various statins, highlighting their differences and similarities.

These conjugation therapies not only lower LDL-C more effectively but also reduce inflammation and stabilize plaques, making them superior to conventional approaches. This review will explore the advancements in drug conjugation strategies within statin therapy, focusing on their potential to enhance the efficacy and safety of these medications.[12–14] By analyzing various techniques, such as polymer-based and nanoparticle-based conjugations, this review aims to highlight how these innovations can optimize statin, offering improved outcomes for patients suffering from atherosclerosis while minimizing adverse effects.[15,16]

2. Conjugation synthesis of statins drug

Conjugation synthesis of statins involves the chemical attachment of statins to carriers, such as polymers, lipids, or bioactive molecules, with the aim of enhancing drug performance. This approach not only improves the pharmacokinetic properties

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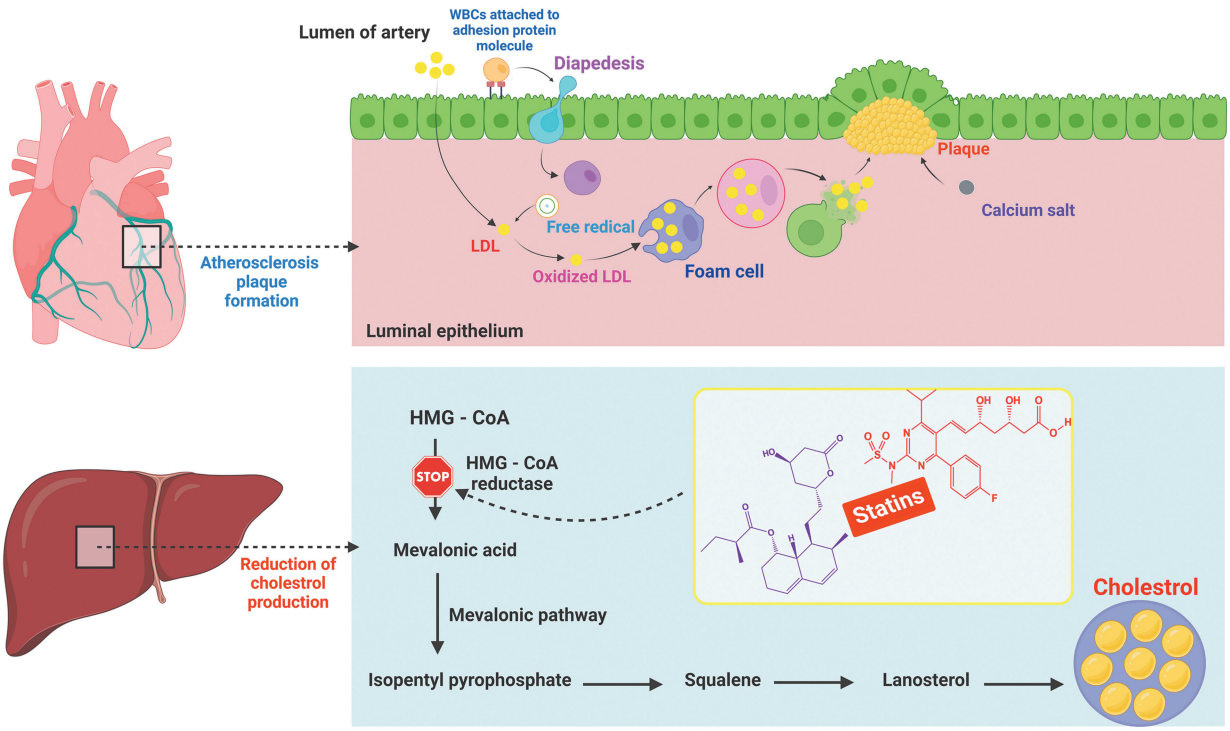

Figure 1: The role of statins in inhibiting cholesterol synthesis and reducing atherosclerosis plaque. HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A; LDL: Low-density lipoprotein; WBCs: White blood cells.

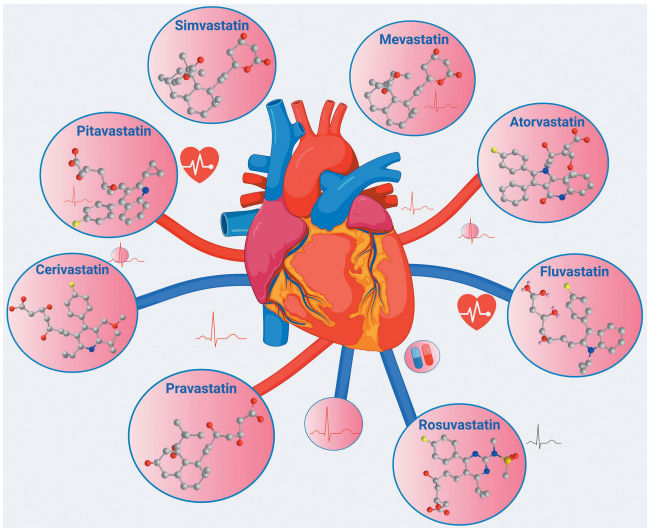

Figure 2: Chemical structures of different statins used in the treatment of cardiovascular diseases.

of statins but also enables precise targeting and controlled release while minimizing adverse effects.[17,18] By increasing solubility, stability, and selective accumulation in atherosclerotic plaques, conjugated statins provide an advanced approach for cardiovascular treatment [Figure 3]. Various strategies, including chemical and biological conjugates, are being explored to optimize the therapeutic potential and delivery of statins, thereby improving their efficiency in clinical applications. Conjugation synthesis offers distinct advantages over traditional oral or intravenous statins delivery methods by enabling targeted and sustained drug release.[19–21] For instance, nanoparticle-based conjugates can bypass rapid clearance mechanisms and deliver statins directly to atherosclerotic plaques, thereby reducing off-target effects and improving therapeutic outcomes.[22]

3. Clinical relevance of conjugation strategies in statin therapy

The novel conjugation strategies for statin delivery hold substantial promise in addressing the limitations of conventional therapies for atherosclerosis. Although traditional statins therapies are effective in lowering LDL-C, they face challenges such as poor solubility, rapid clearance, and nonspecific systemic distribution, often resulting in adverse effects such as myopathy and hepatotoxicity. Randomized clinical trials and preclinical studies have highlighted the advantages of these advanced conjugation strategies. To illustrate these findings, Table 1 provides a summary of the clinical utility and benefits of various conjugation strategies.[23–37]

4. Chemical conjugation

Chemical conjugation refers to the covalent bonding of 2 or more molecules to form a single complex. This process typically involves attaching a bioactive molecule (eg, a drug) to a carrier molecule (eg, a polymer, protein, or antibody) using chemical linkers. The aim is to enhance the stability, solubility, or targeting capabilities of the active molecule, allowing for improved therapeutic efficacy and reduced off-target effects [Figure 4].[16–18]

5. Biological conjugation

Biological conjugation refers to modern techniques that exploit the inherent specificity of biological molecules such as proteins, peptides, or antibodies. By leveraging these receptor-targeting properties, biologically active substances can be directed with higher precision to specific tissues or disease sites.[34,37] For example, in cardiovascular therapy, biological conjugation techniques can direct statins towards atherosclerotic plaques. This targeted approach increases the concentration of the drug in areas of plaque buildup, thus improving efficacy while minimizing potential side effects elsewhere in the body [Figure 5].[22,35]

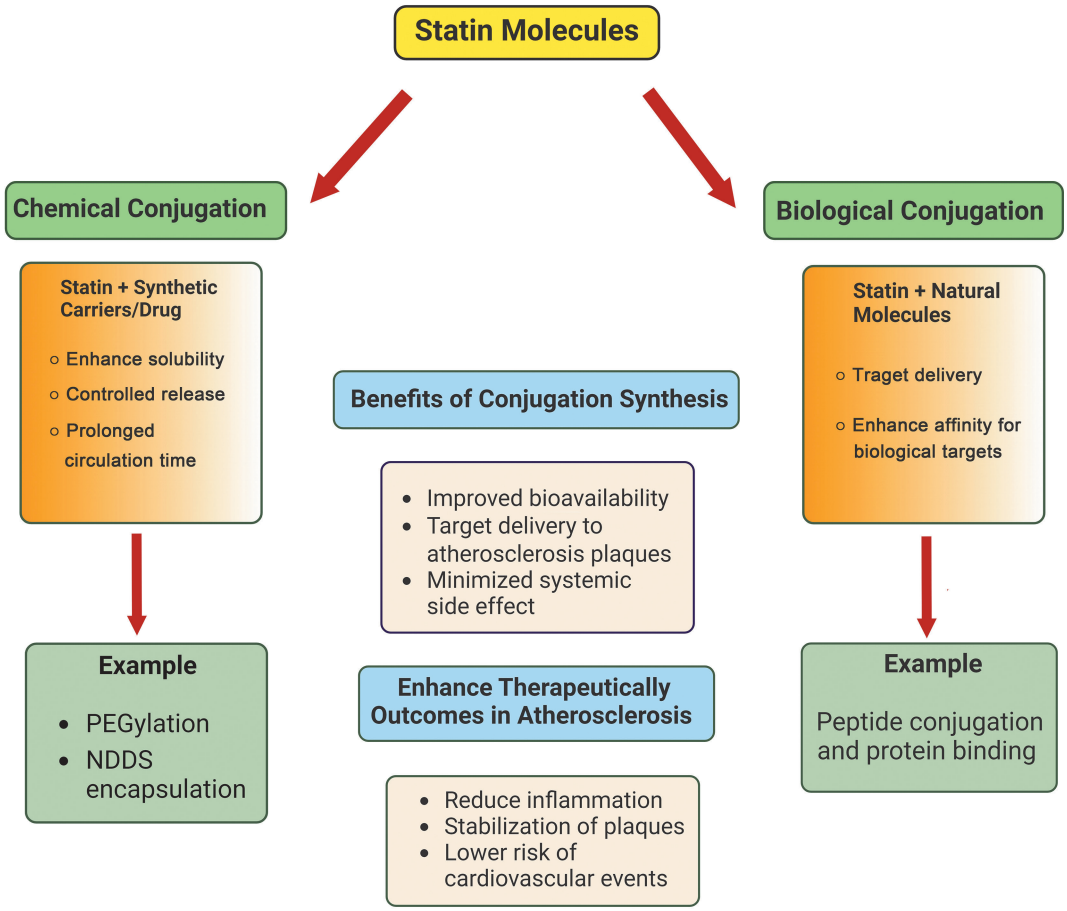

Figure 3: Conjugation strategies of statin molecules for atherosclerosis therapy. NDDS: Novel drug delivery systems; PEGylation: Polyethylene glycolylation.

Table 1

Clinical relevance of conjugation strategies in statins therapy.

Therapy type	Mechanism and supporting evidence	Benefits
Polymer-based conjugation[23–25]	Sustained drug release and improved bioavailability studies	Reduced dosing frequency and enhanced stability
Nanoparticle-based conjugation[26–28]	Targeted delivery to atherosclerosis plaques reduced plaque size and inflammation *in vivo*	Site-specific delivery minimized systemic exposure
Peptide- and protein-based conjugation[29–31]	Effective in reducing plaque formation and improving cardiovascular outcomes in preclinical studies	Enhanced efficacy potential for personalized therapy
Liposome-based conjugation[32,33]	Enabled effective encapsulation of statins, enhancing delivery to vascular tissues in clinical settings	Provided superior stability and prolonged circulation time compared to non-liposomal delivery methods
Antibody-drug conjugation[34,35]	Targeted immunotherapy approaches reduced LDL-C levels significantly in phase II clinical trials	Higher specificity and fewer off-target effects compared to conventional therapies
Micelle-based conjugation[36,37]	Enhanced solubility of poorly water-soluble statins as demonstrated in early clinical studies	Improved bioavailability and tunable release rates, offering flexibility in dose adjustments compared to standard statin medications

LDL-C: Low-density lipoprotein cholesterol.

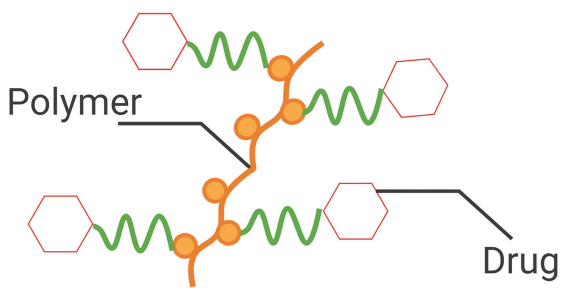

Figure 4: Schematic representation of a chemical conjugate.

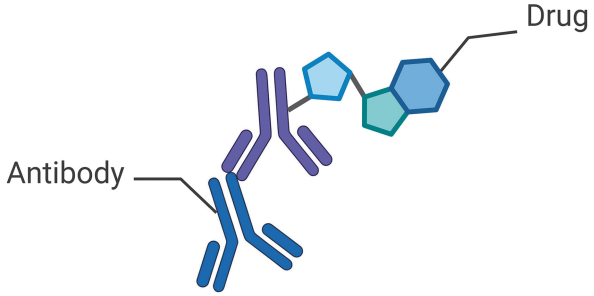

Figure 5: Schematic representation of a biological conjugate.

6. Current strategies in conjugation synthesis

Current strategies in conjugation synthesis focus on enhancing the therapeutic potential of statins by improving their delivery and effectiveness. Key approaches include polymer-based conjugates, nanoparticle-based conjugation, and protein- and peptide-based conjugation.

6.1. Polymer-based conjugation

Polymer-drug conjugates are an innovative strategy in drug delivery, utilizing a biocompatible outer shell that encapsulates the drug within an inner core. These systems enhance the stability and efficacy of drugs administered via both oral and non-oral administration. In oral delivery, the dense outer shell limits gastrointestinal absorption, prolongs systemic circulation and enables controlled, sustained release.[15,33] For non-oral routes, the shell protects the drug from enzymatic degradation, ensuring its stability until it reaches the target site. This approach is particularly effective in delivering statins in the treatment of coronary artery disease, improving bioavailability, and reducing side effects [Figure 6].

In a 2013 study, Zhou et al[23] explored the synthesis and characterization of dextran-rosuvastatin conjugates for drug delivery. Rosuvastatin's low oral bioavailability prompted this approach, where dextran was conjugated using N,N-carbonyldiimidazole, forming self-assembling microparticles. Particle size and morphology were controlled by solvent and pH conditions. Characterization by Fourier transform infrared spectroscopy, nuclear magnetic resonance spectroscopy, X-ray diffraction confirmed the synthesis, and *in vitro* studies showed sustained release with morphology-dependent kinetics, suggesting dextran-rosuvastatin conjugates's potential for enhanced therapeutic efficacy [Figure 7].

In 2011, Anwar et al[24] developed a chitosan-atorvastatin nano-conjugate to improve atorvastatin's bioavailability and stability [Figure 8]. The conjugate, synthesized via amide coupling and characterized by proton nuclear magnetic resonance and Fourier transform infrared spectroscopy, produced nano-sized particles ((215.3 ± 14.2) nm) via high-pressure homogenization. *In vitro* release studies revealed sustained release, while pharmacokinetic studies showed a 5-fold bioavailability increase compared to pure atorvastatin, indicating the potential of chitosan conjugates to oral drug delivery.

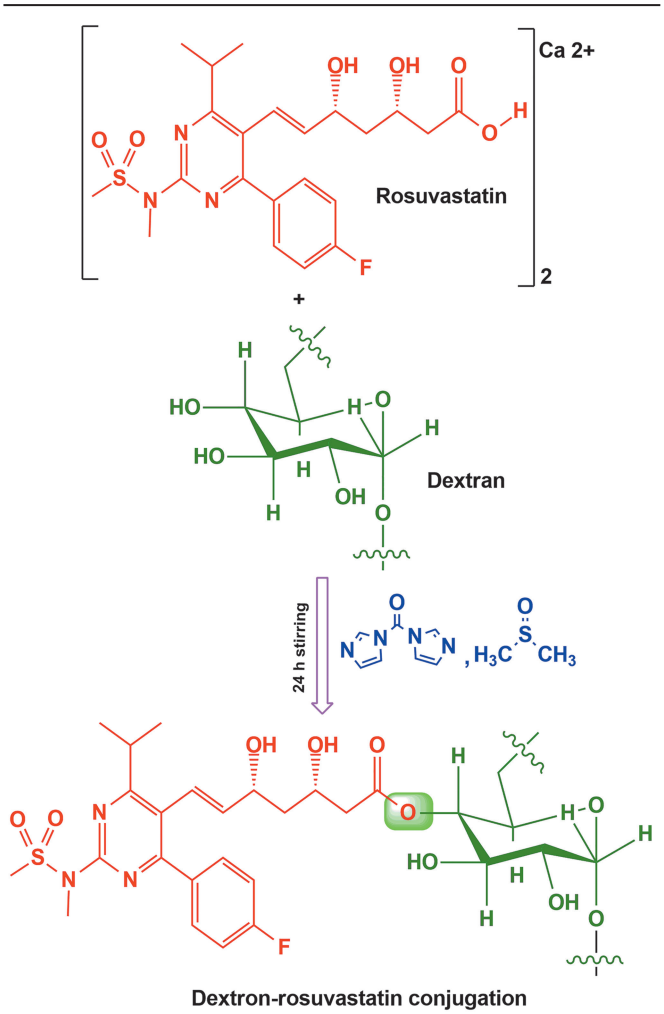

Figure 7: Synthesis and self-assembly of dextran-rosuvastatin conjugate microparticles.

Recently, Hossaini Nasr et al[25] synthesized hyaluronic acid-atorvastatin conjugate nanoparticles to target inflammation in atherosclerotic plaques. These nanoparticles with hydrophobic cores of atorvastatin surrounded by hydrophilic

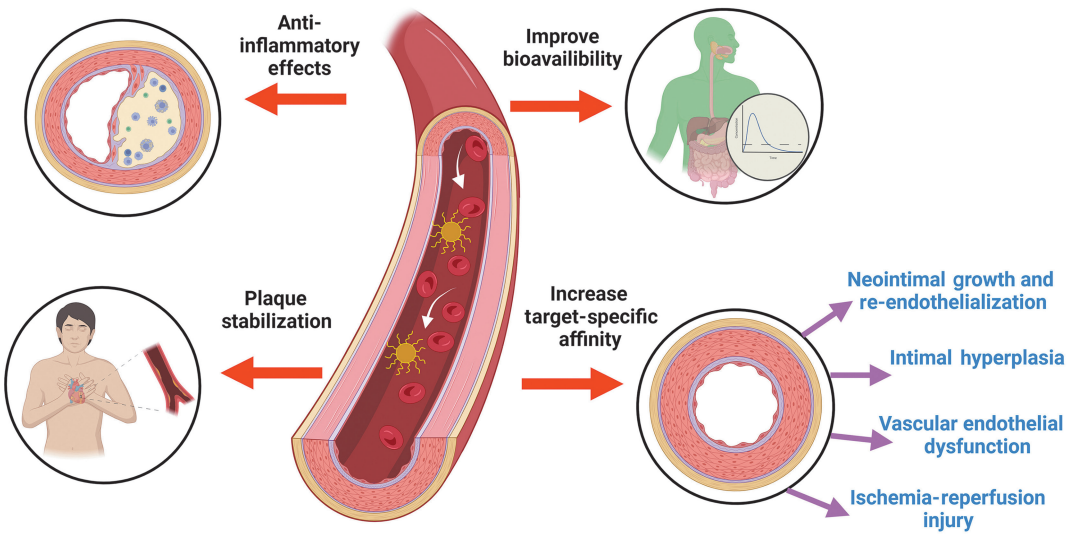

Figure 6: Anti-inflammatory effects, plaque stabilization, bioavailability improvement, and target-specific affinity in vascular systems, facilitated by polymer-based conjugation strategies.

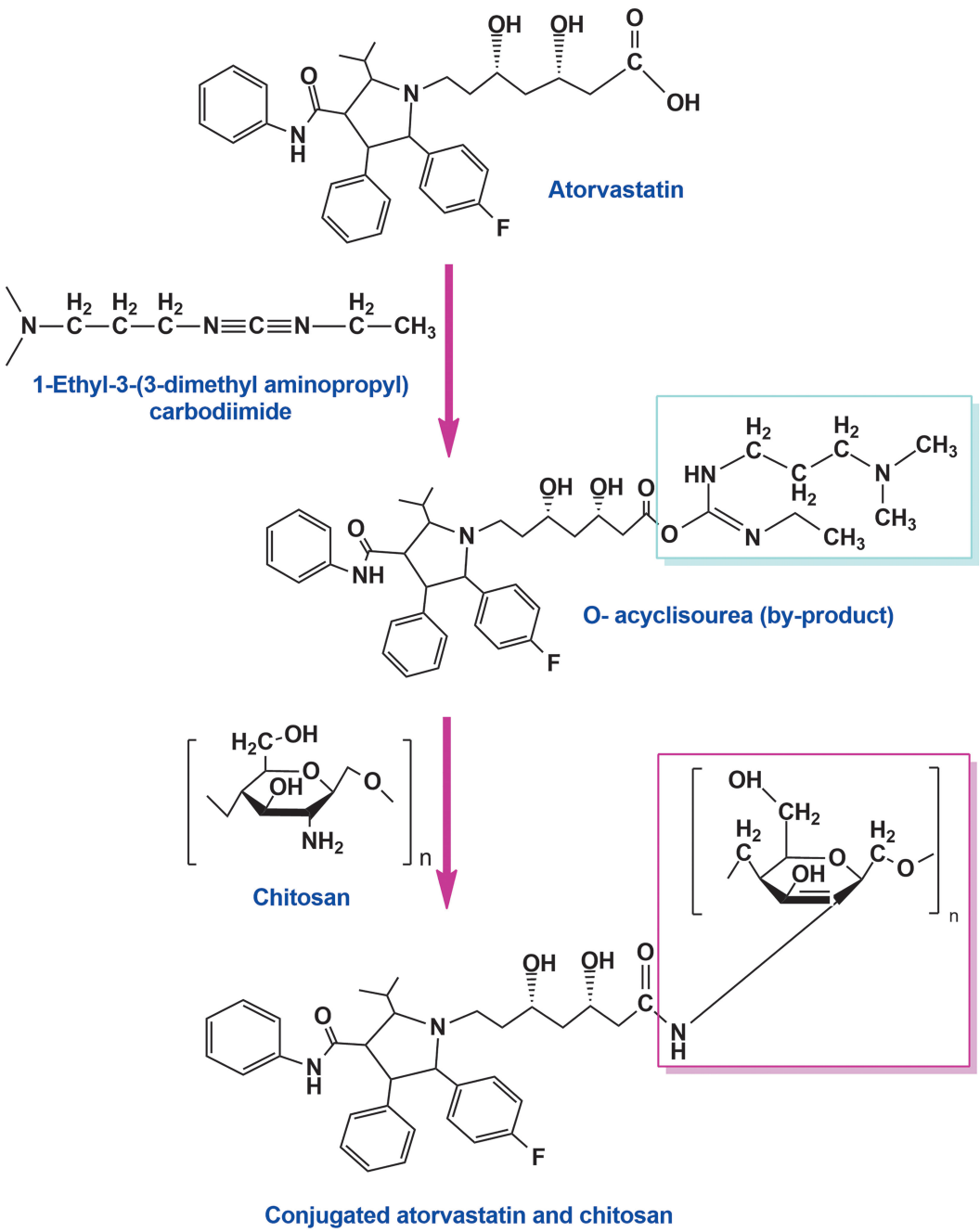

Figure 8: Synthesis of chitosan-atorvastatinnano-conjugate via amide coupling reaction.

hyaluronic acid, showed superior drug loading, stability, and CD44 receptor-mediated targeting. *In vitro*, the nanoparticles inhibited inflammatory responses in macrophages, and *in vivo*, they reduced plaque size and inflammation in mice more effectively than free atorvastatin, suggesting a promising anti-inflammatory approach for atherosclerosis [Figure 9].

6.2. Nanoparticle-based conjugation

Nanoparticle-based therapies have shown sustained effectiveness over time, they offer a promising strategy for selectively inhibiting macrophage activity, which serve as a potential therapeutic target for treating inflammation in atherosclerosis. By targeting the cellular and molecular mechanisms that contribute to plaque formation and instability, these advanced nanotherapies may provide a more localized and effective treatment option, potentially improving clinical outcomes for patients with advanced atherosclerosis [Figure 10].[26–27]

A study conducted by Gao et al[28] introduced macrophage membrane-coated, reactive oxygen species-responsive nanoparticles for targeted atorvastatin delivery in atherosclerosis. These nanoparticles selectively target activated macrophages at plaque sites, evading the reticuloendothelial system. The therapeutic benefits include reduced plaque vulnerability, increased collagenand deposition, decreased matrix metalloproteinase activity, and improved lipid profiles. Also, the microphage membrane coating sequesters pro-inflammatory cytokines, reducing local inflammation and enhancing therapeutic efficacy [Figure 11].

In 2013, Dash et al[32] developed atorvastatin-curcumin nanocrystals with synergistic anti-inflammatory effects. In-silico

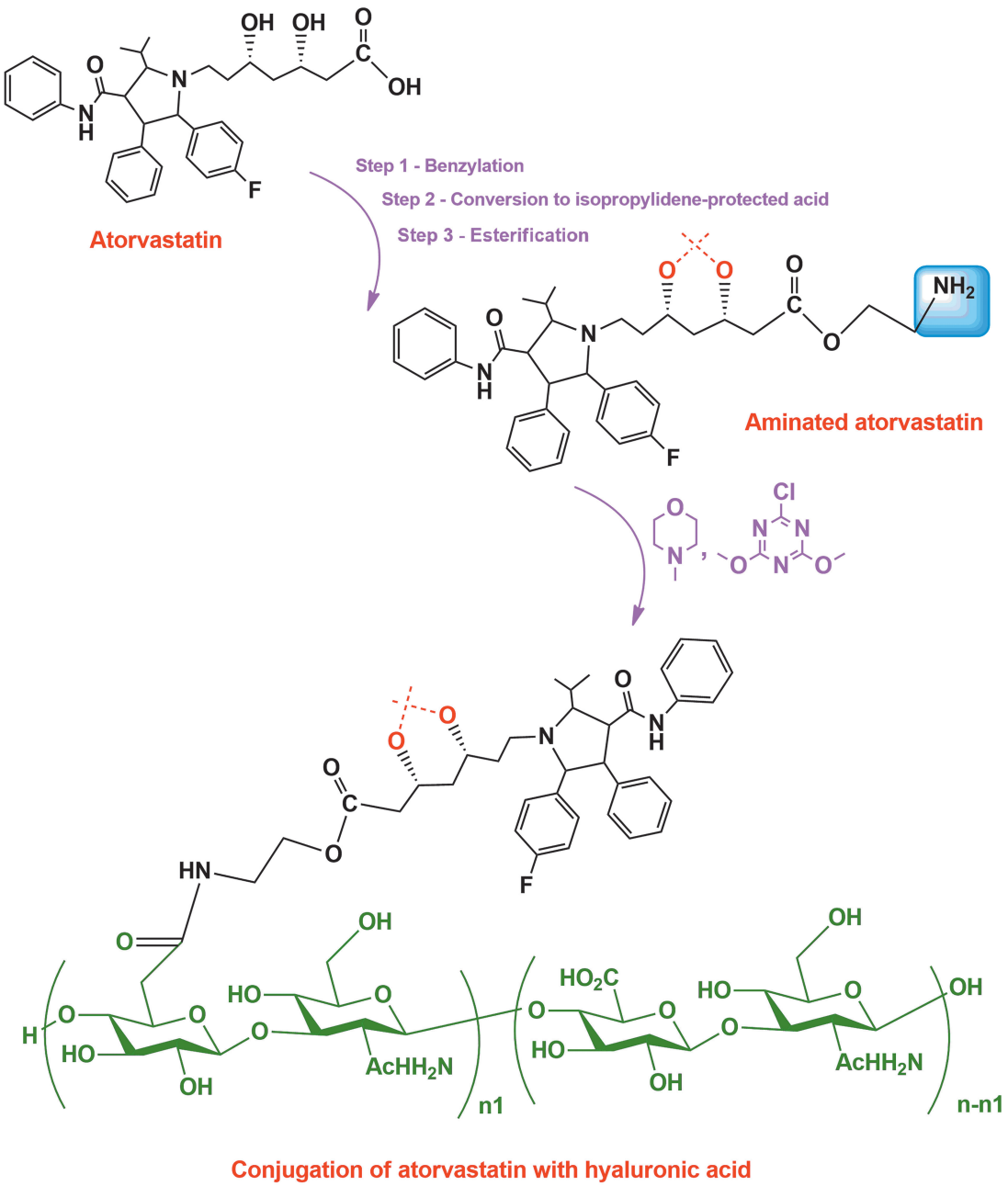

Figure 9: Hyaluronic acid-atorvastatin conjugate nanoparticles.

analysis showed a high affinity for COX-1 and COX-2 enzymes. The nanocrystals characterized by zeta potential of –35 mV, exhibited improved solubility and stability. Formulated as an emulgel, they provided sustained release for 28 h and showed strong anti-inflammatory responses *in vivo*. The study highlights atorvastatin-curcumin nanogel as a potential alternative to nonsteroidal anti-inflammatory drugs [Figure 12].

6.3. Peptide- and protein-based conjugation

Recent research has highlighted the potential of conjugating peptide with statins as a targeted strategy against atherosclerosis, demonstrating promising results in reducing plaque formation and improving cardiovascular health. Peptides, especially those mimicking apolipoprotein A-I (ApoA-I), have been shown to effectively reduce inflammation and improve lipid profiles when used in statinconjugates. This combination leverages the anti-inflammatory properties of peptides and the cholesterol-lowering effects of statins, potentially offering a synergistic approach to treat atherosclerosis.[33] For example, Duivenvoorden et al[30] developed reconstituted high-density lipoprotein (HDL) nanoparticles for simvastatin delivery in atherosclerosis. By using ApoA-I and phospholipids, lipophilic simvastatin was encapsulated in discoid nanoparticles (25–30 nm), which were stabilized to resist degradation in serum. Magnetic resonance imaging contrast agents and dyes were added for imaging, forming a stable system targeting atherosclerotic plaques. Another conducted in 2015, Tang et al[31] developed simvastatin-loaded HDL nanoparticles for targeting atherosclerotic plaques. By integrating simvastatin with phospholipids and ApoA-I, simvastatin-loaded HDL mimicked natural HDL, stabilizing the drug and enabling penetration into plaques. This system reduced macrophage proliferation and inflammation, enhancing plaque targeting and therapeutic outcomes [Figure 13].

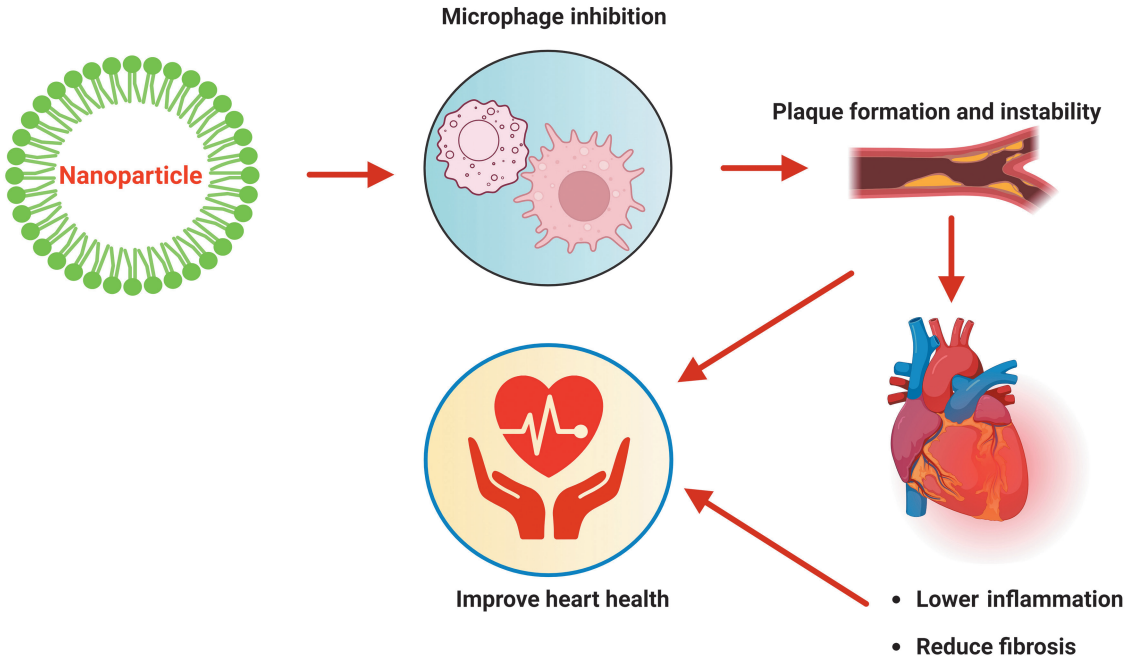

Figure 10: Nanoparticle-mediated macrophage inhibition, plaque formation, and improved heart health outcomes.

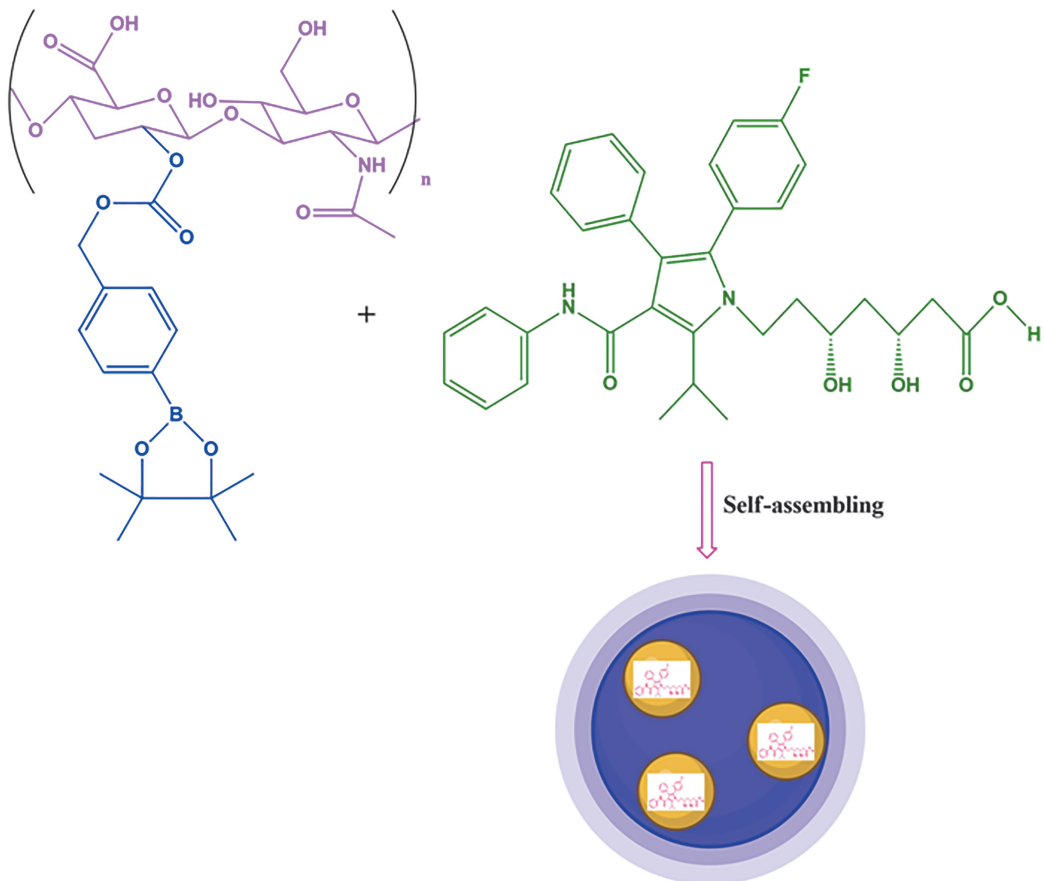

Figure 11: Macrophage membrane-coated reactive oxygen species-responsive nanoparticles for targeted delivery of atorvastatin.

7. Application of conjugation strategies in statins therapy

Conjugation strategies have emerged as a promising method to enhance the therapeutic potential of statins by addressing several limitations of traditional treatments. By chemically conjugating statins with polymers, nanoparticles, or bioactive molecules, their bioavailability can be greatly improved, leading to better drug absorption and enhanced therapeutic effects.[35]

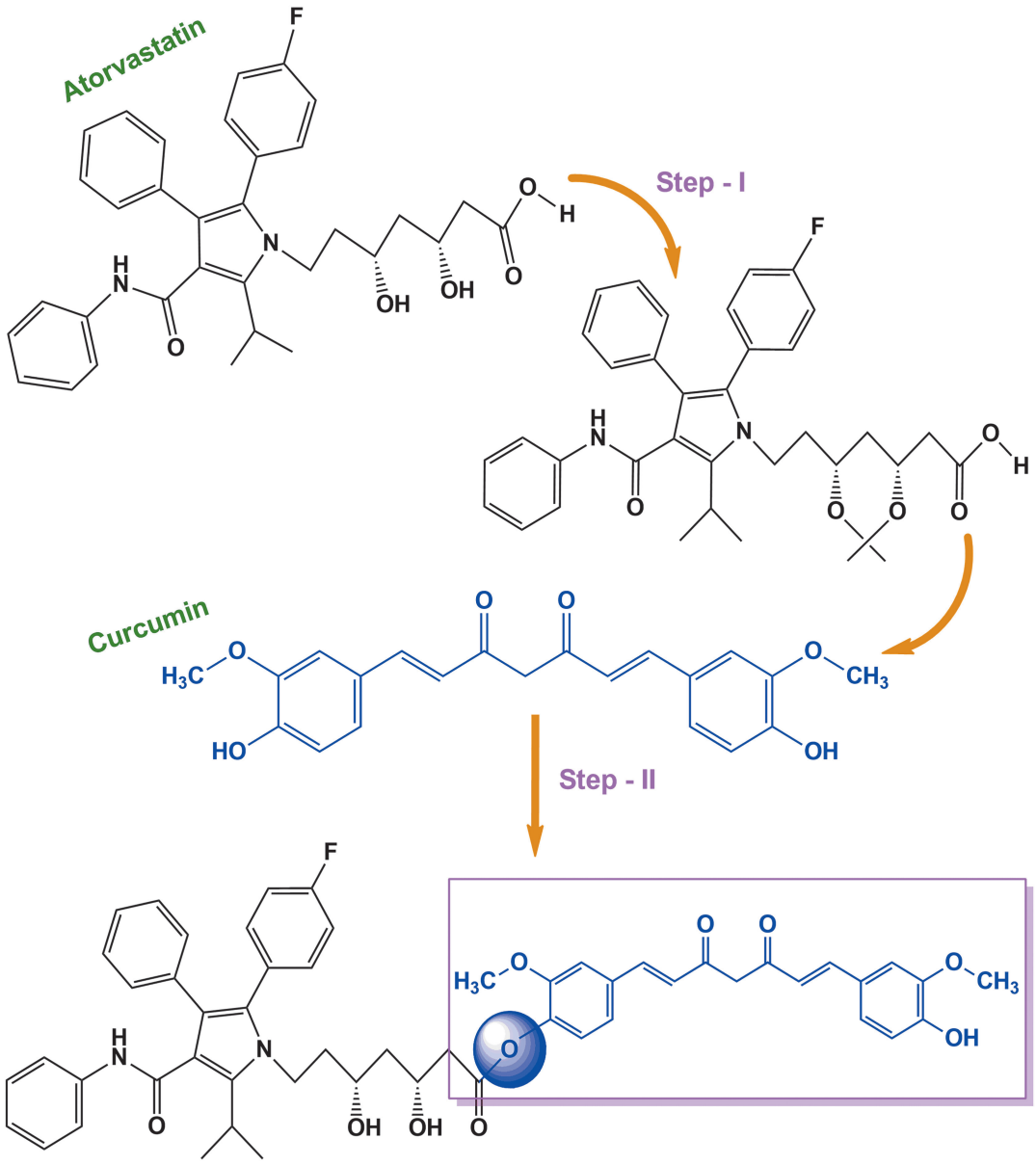

Figure 12: Conjugation of atorvastatin with curcumin by estrification method.

One significant advantage of conjugation is its ability to facilitate targeted drug delivery, allowing statins to be directed specifically to atherosclerotic plaques. This targeted approach reduces systemic exposure and minimizes undesirable side effects. Additionally, conjugation improves cellular uptake, enabling statins to more effectively penetrate target tissues, thereby boosting their therapeutic efficacy.[38] Conjugated systems also extend the circulation time of statins in the bloodstream, ensuring sustained drug levels, reducing the frequency of dosing, and promoting longer-lasting therapeutic benefits. Collectively, these conjugation techniques represent a powerful strategy for optimizing statin therapies and overcoming the challenges associated with conventional treatments for atherosclerosis.[39]

8. Challenges and limitations of conjugation method

In the conjugation strategies for atherosclerosis therapies, several challenges and limitations need to be addressed to ensure the efficacy and safety of these next-generation treatments. One of the key challenges lies in maintaining the stability of conjugated drug systems under physiological conditions.[40] Factors such as enzymatic activity, fluctuating pH levels, and interactions with proteins in the bloodstream can lead to premature degradation or destabilization of the conjugated molecules, thereby reducing their therapeutic effectiveness.[41,42] Additionally, the potential immunogenicity of foreign polymers, nanoparticles, or bioactive

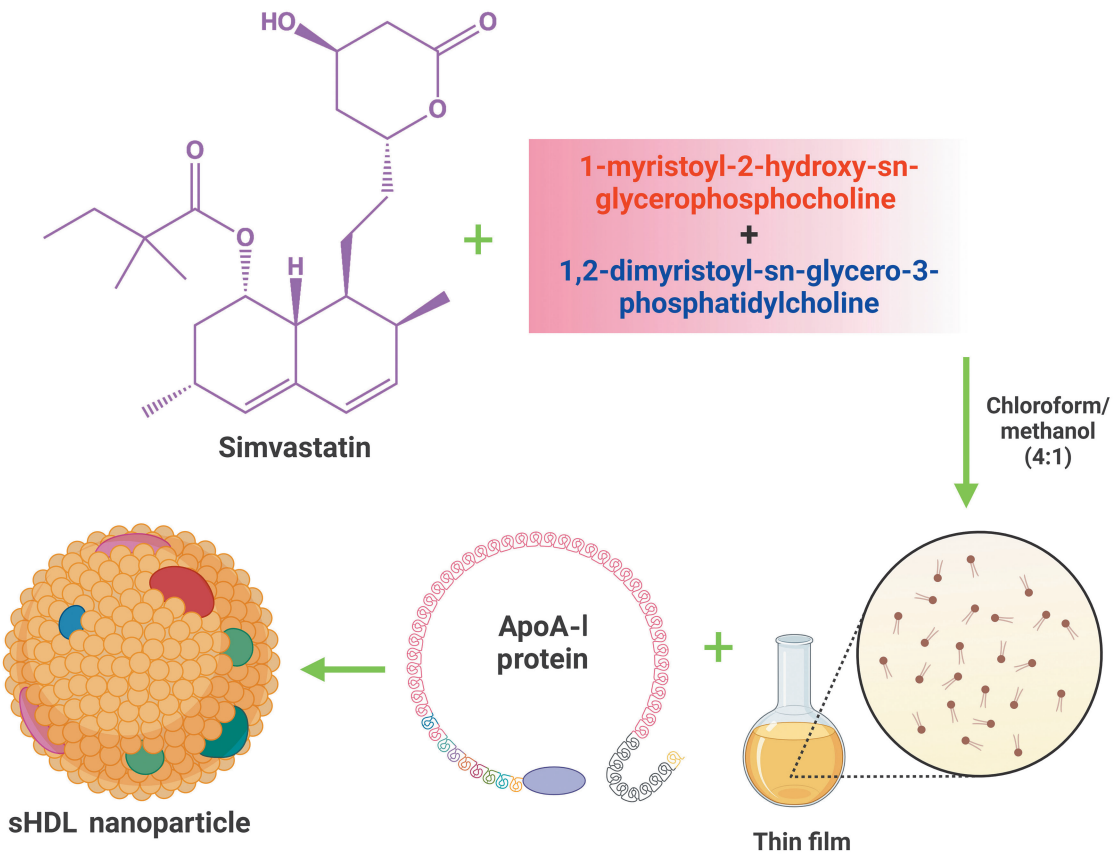

Figure 13: sHDL nanoparticles is constructed by integrating simvastatin with phospholipids and ApoA-I. ApoA-I: Apolipoprotein A-I; sHDL: Simvastatin loaded high-density lipoprotein.

molecules used in conjugation poses a risk of eliciting immune responses, which may result in adverse reactions and compromise the overall safety of the treatment.[43] Another significant limitation is the complexity of pharmacokinetics in conjugated systems. The chemical modifications introduced during conjugation can alter the absorption, distribution, metabolism, and excretion of statins, leading to variability in therapeutic outcomes. This unpredictability in pharmacokinetics makes it challenging to optimize dosing regimens and predict patient responses. Addressing these challenges is crucial to advancing conjugation strategies and ensuring their successful application in atherosclerosis treatment.[44,45]

9. Conclusion

The advancements in conjugation synthesis of statins present significant preclinical benefits, their potential impact in clinical settings should not be overlooked. Conjugated statins are poised to offer several key advantages over traditional statin therapies. Enhanced drug delivery mechanisms improve solubility, stability, and bioavailability, ensuring that the drug is more effectively targeted to atherosclerotic plaques. This targeted approach not only amplifies the therapeutic benefits, such as LDL reduction and plaque stabilization, but also significantly reduces systemic side effects, which remain a major concern with conventional statins use. Moreover, these advancements pave the way for more personalized treatment regimens, allowing therapy to be tailored to the specific needs of individual patients, particularly those who are statin-intolerant or exhibit genetic variability in response to treatment. While these promising outcomes have been demonstrated in preclinical studies, further research, including clinical trials, is necessary to validate these benefits in human populations and to fully understand the long-term implications of conjugated statin therapies. Despite these challenges, conjugated statins represent a significant leap forward in the management of atherosclerosis, offering improved drug delivery and reduced systemic side effects. The potential for these therapies to deliver personalized treatment solutions, particularly in patients with statin intolerance or genetic variability, underscores their importance in the future of cardiovascular disease management. As research progresses, the translation of these preclinical advantages into clinical success will be a key area of focus.

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Author contributions

Varsha Rawat conceptualized the study, conducted the literature review, and drafted the manuscript. Smriti Dewangan, Khomendra Kumar Sarwa, and Tripti Sharma contributed to the review, editing, and refinement of the manuscript. All authors approved the final version and are accountable for the content.

Conflicts of interest

None.

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