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REVIEW

Formulation Strategies for Ezetimibe and Its Combinations: Advancing Biopharmaceutical and Therapeutic Potential

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Abstract: Ezetimibe is a cholesterol absorption inhibitor widely used in the treatment of dyslipidemia. However, its clinical efficacy is limited by poor aqueous solubility and low oral bioavailability. Therapeutic guidelines on dyslipidemia recommend ezetimibe as an adjunct or alternative to statins, particularly in patients who are intolerant to high-dose statins or have inadequate LDL-C reduction. This review summarizes recent advances in ezetimibe formulations, including single-active and combination systems, and discusses their effects on solubility, pharmacokinetics, and therapeutic outcomes. The analysis is based on literature published within the last decade (2015–2025) from reputable scientific databases. Advanced strategies such as solid-state modification, particle size reduction, and lipid or surfactant-based delivery systems have significantly enhanced drug dissolution. In vivo studies report relative bioavailability improvements of approximately 120 to 800% compared to pure drug suspensions/marketed products, translating into favorable pharmacodynamic profiles. Beyond single-active systems, innovative co-delivery with statins such as simvastatin, atorvastatin, rosuvastatin, and lovastatin has demonstrated added pharmacological synergy and supports the development of fixed-dose combination products. Collectively, these advances provide strong evidence that optimized ezetimibe formulations in single-active or combination systems have strong potential to improve the biopharmaceutical profile and future therapeutic application in dyslipidemia management.

Keywords: ezetimibe, formulation design, fixed dose combination, drug release, biopharmaceutical performance

Introduction

Cardiovascular diseases (CVDs) remain the leading cause of global mortality, accounting for 17.9 million deaths or 32% of all deaths worldwide in 2019, according to the World Health Organization (WHO).[1] Among the various risk factors, dyslipidemia, characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C) and other atherogenic lipoproteins, plays a central role in the development of atherosclerotic cardiovascular disease (ASCVD).[2–5] The accumulation of apolipoprotein B (ApoB)- containing lipoproteins, such as LDL, within the arterial wall accelerates atherosclerosis, reinforcing LDL-C reduction as a primary target in cardiovascular risk management.[6–8] Current clinical guidelines recommend statins as the first-line therapy due to their well-established efficacy in lowering LDL-C by inhibiting hepatic cholesterol biosynthesis and upregulating LDL receptors.[9,10] Despite their proven efficacy and widespread use, not all patients tolerate statins or reach LDL-C goals with statin monotherapy. In such cases, non-statin therapies serve as essential alternatives or adjuncts to statin therapy.[11–13]

Among non-statin agents, ezetimibe holds a unique and pivotal role. It is the only FDA-approved cholesterol absorption inhibitor (CAI), which selectively blocks the Niemann-Pick C1-Like 1 (NPC1L1) transporter in the small intestine, thereby inhibiting cholesterol absorption.[14,15] Ezetimibe can reduce LDL-C by 15–25%, and is well-tolerated

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with a favorable safety profile.[13,16,17] The ESC (European Society of Cardiology) and EAS (European Atherosclerosis Society) Guidelines (2019) recommend ezetimibe as the preferred non-statin option for combination therapy or as monotherapy in individuals who are statin-intolerant.[18] Similarly, the 2018 guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA) recommended adding ezetimibe in patients with ASCVD who do not achieve LDL-C goals on statin monotherapy.[19] The use of ezetimibe has increased significantly in recent years. For example, data from Germany demonstrated a fivefold increase in ezetimibe monotherapy prescriptions between 2012 and 2021.[20] Ezetimibe offers substantial economic and practical advantages compared to other non-statin therapies, such as PCSK9 inhibitors and bempedoic acid.[21]

Currently, ezetimibe is available as a 10 mg oral tablet, either as a single compound or in fixed-dose combinations with various statins as well as with newer agents, including bempedoic acid.[22] Ezetimibe is a Biopharmaceutics Classification System (BCS) Class II compound, characterized by low water solubility, which affects its dissolution and bioavailability.[17] The oral bioavailability of ezetimibe is approximately 35%, primarily due to its low solubility and P-gp (P-glycoprotein) efflux.[23,24] These limitations may contribute to variability in therapeutic response, with some patients requiring combination therapy to achieve recommended LDL-C targets. This has driven the development of various formulation strategies aimed at enhancing dissolution, reducing P-gp efflux, and improving bioavailability.[17,25] Multiple delivery approaches have been explored for ezetimibe, including solid-state modification, lipid-based delivery systems, and particle size reduction techniques. One example is the development of ezetimibe-loaded solid lipid nanoparticles (SLNs), which exhibited a sixfold increase in in vitro dissolution compared to the pure drug and a twofold increase in the dissolution rate compared to the marketed formulation. In vivo, this formulation enhanced systemic exposure, with Cmax and AUC increasing by 2.6- and 3.3-fold, respectively, compared to the marketed product, and by 11.6- and 8.7-fold compared to a conventional suspension.[26]

The current formulation development of ezetimibe extends beyond its use as monotherapy and includes its incorporation into combination therapies with other lipid-lowering agents. As ezetimibe is primarily used as an adjunct to statins, it has increasingly been developed in the form of fixed-dose combinations. These formulations aim to enhance therapeutic synergy, improve patient adherence, and optimize pharmacokinetic and pharmacodynamic profiles, especially when designed to overcome their poor solubility and limited bioavailability.[22,27]

Despite over two decades of clinical use, comprehensive reviews focusing on advanced formulation strategies for ezetimibe, either alone or in combination, remain lacking. Additionally, the effects of these innovative systems on drug release, pharmacokinetics, and therapeutic outcomes are yet to be fully elucidated. This review aims to bridge these gaps by summarizing recent advancements in the formulation of ezetimibe and its combinations, evaluating their biopharmaceutical performance, and exploring their therapeutic implications in the management of dyslipidemia. The review is based on literature published within the last decade (2015–2025), selected from reputable scientific databases, including PubMed, ScienceDirect, Taylor & Francis, SpringerLink, and Scopus.

Biopharmaceutical Basis and Challenges of Ezetimibe

Ezetimibe is classified as a BCS Class II drug because its crystalline aqueous solubility is extremely low (≈ 0.008 mg/mL at 25 °C) and its lipophilicity is high (log P ≈ 4.5).[28,29] Even in biorelevant fasted-state intestinal fluid (FaSSIF), the solubility rises only to ≈ 11–12 μg/mL, confirming that dissolution limits oral uptake.[29] Conversely, Caco-2 cell studies have reported an apparent permeability coefficient in the range of 2.7 to 3.0×10^{-6} cm/s, which supports the classification of ezetimibe as a highly permeable compound.[30] Despite its adequate permeability, the absolute oral bioavailability remains modest and variable (35–65%), mainly due to slow dissolution and extensive pre-systemic metabolism.[28]

Following oral administration, ezetimibe undergoes rapid and extensive Phase II metabolism, primarily glucuronidation by UGT isoforms (UGT1A1, UGT1A3, and UGT2B15), yielding ezetimibe-glucuronide (EZE-G), the pharmacologically active metabolite. Peak plasma concentrations of ezetimibe and its glucuronide are generally observed within 2–3 hours. EZE-G accounts for approximately 90% of the circulating drug-related material, emphasizing its dominant role in mediating the lipid-lowering effect. A unique feature of ezetimibe pharmacokinetics is its extensive enterohepatic recycling. Once glucuronidated in the liver, EZE-G is transported into bile via MRP2 (ABCC2) and stored in the gallbladder. After food intake, it is released into the intestine, where intestinal β-glucuronidase enzymes regenerate the

parent drug, allowing it to be reabsorbed. This recycling process contributes to multiple peaks in plasma concentration-time profiles and prolongs systemic exposure. In parallel, intestinal P-glycoprotein (P-gp) can limit absorption by promoting efflux, while OATP1B1 in hepatocytes facilitates the hepatic uptake of EZE-G. Genetic polymorphisms in these transporters have been linked to altered pharmacokinetic profiles and interindividual variability in response to therapy.[31–33]

Ezetimibe's effective elimination half-life of approximately 22 hours allows for convenient once-daily dosing at 10 mg. The drug is primarily excreted via the feces (~78%), while a smaller fraction (~11%) is eliminated in the urine, predominantly as ezetimibe-glucuronide. Despite its favorable attributes, such as high permeability and a long half-life, ezetimibe's clinical performance is constrained by poor aqueous solubility, rapid pre-systemic metabolism, and complex transporter interactions, which contribute to variable absorption and therapeutic response. Moreover, due to enterohepatic cycling, its multiple-peak pharmacokinetic profile can mask formulation-dependent effects, making bioavailability optimization more challenging.[31–33]

Formulation Approaches to Enhance the Solubility of Ezetimibe in Single-Active Formulations

Ezetimibe is a BCS Class II drug whose primary limitation in oral delivery lies in its extremely low aqueous solubility. Although it exhibits high intestinal permeability, its poor dissolution in gastrointestinal fluids significantly restricts its rate and extent of absorption, leading to variable and suboptimal bioavailability. As a result, formulation strategies have primarily focused on improving solubility and dissolution rates in the gastrointestinal tract, aiming to enhance systemic exposure and therapeutic consistency. Recent formulation approaches for ezetimibe in a single active system can be categorized into three primary directions: solid-state modification, nanosizing techniques, and lipid/surfactant-based delivery systems. Figure 1 provides a comprehensive overview of the formulation strategies developed for ezetimibe.

Solid State Modifications

Solid-state modifications focus on altering the crystalline nature of ezetimibe to improve its solubility and dissolution rate.[34] This includes the development of amorphous solid dispersions, co-crystals, inclusion complexes, and eutectic mixtures. By reducing crystal lattice energy or improving molecular interactions with carriers, these strategies lower the thermodynamic stability of the drug and facilitate faster dissolution in the gastrointestinal tract. Figure 2 illustrates ezetimibe incorporated in various solid-state modification systems.

Solid Dispersion

Solid dispersion is a well-established strategy in pharmaceutical science to improve the solubility, dissolution rate, and oral bioavailability of poorly water-soluble drugs.[35] This technique involves dispersing the drug into a hydrophilic polymer matrix. The resulting system can transform the crystalline drug into a more soluble amorphous form or create a molecular-level dispersion within the carrier matrix. These transformations enhance the dissolution in the gastrointestinal tract, potentially improving absorption and therapeutic effect.[36]

Several studies have reported the successful application of solid dispersion systems to enhance the biopharmaceutical performance of ezetimibe. For instance, dispersions prepared using polyvinylpyrrolidone K30 (PVP K30) via solvent evaporation have substantially improved ezetimibe's dissolution behavior. Compared to the pure crystalline drug, the dispersion enabled faster and more complete drug release (achieving up to 98% drug release in 10 minutes compared to 47% for the pure drug). These translate into more effective reductions in serum cholesterol levels in animal models.[37] The use of other carriers such as Gelucire 50/13, alone or in combination with PVP K30, has also been investigated through modified solvent evaporation methods. These systems exhibited superior drug release profiles, showing 87.54% drug release within 1 hour, significantly higher than the pure drug (24.67%, $p < 0.05$).[38]

Another study prepared surface-modified solid dispersions (SMSD) and solvent-evaporated solid dispersions (SESD) by spray-drying using hydroxypropyl cellulose (HPC) and Tween 80. Both dispersions markedly improved aqueous solubility and accelerated early-stage dissolution relative to the crystalline form. Pharmacokinetic testing confirmed a several-fold rise in systemic exposure, with the SESD formulation providing the most significant enhancement.[39] A companion study employed a similar spray-drying process to generate binary (ezetimibe–HPC) and ternary

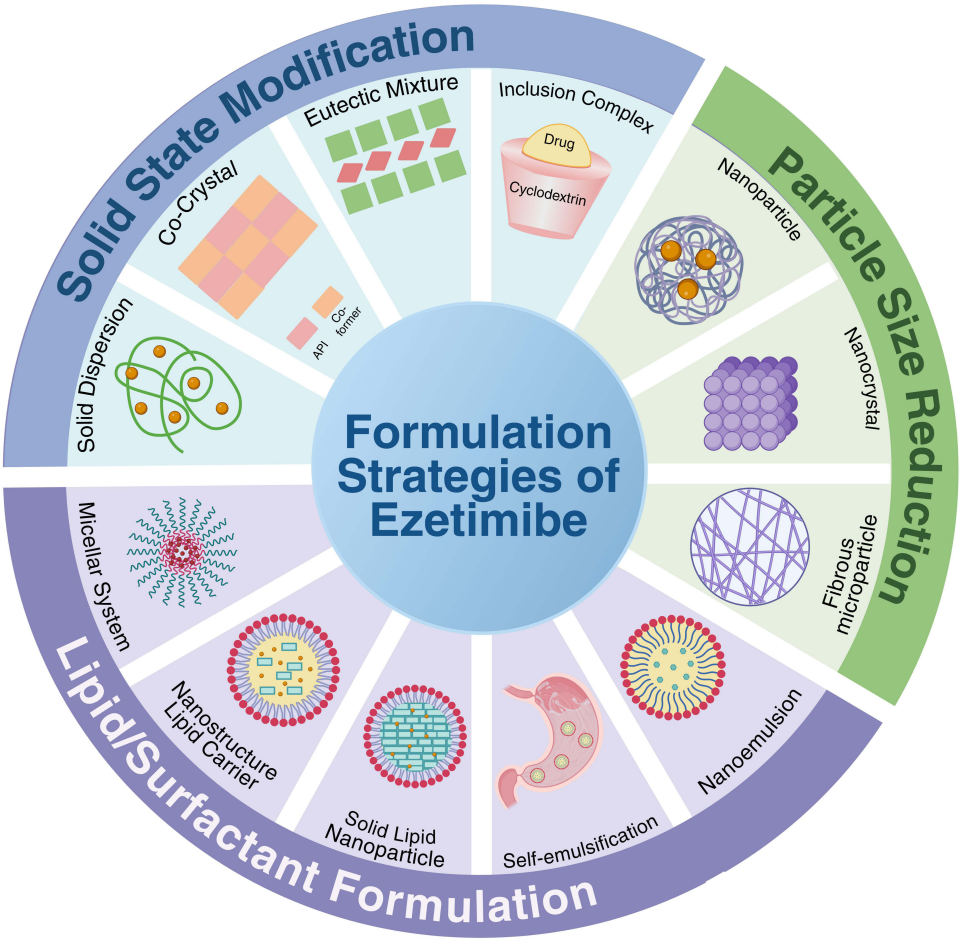

Figure 1 Formulation strategies of ezetimibe. Created in BioRender. Priani, S. (2025) https://BioRender.com/f6gnjfz.

(ezetimibe–HPC-Tween 80) solid dispersions at higher polymer-to-drug ratios. Solid dispersions at a drug/polymer ratio of 1:10 and 1:20 significantly enhanced the dissolution of ezetimibe compared to the pure drug, achieving nearly 100% release within 120 minutes, representing a 5-fold increase in dissolution rate. The system exhibited higher peak plasma concentrations and overall exposure compared to both the pure drug and the binary system.[40]

An innovative approach to enhance ezetimibe's solubility and patient compliance involved incorporating its amorphous solid dispersion into an oral disintegrating film (ODF). The dispersion demonstrated reduced crystallinity and improved dissolution when mannitol was used as the carrier. The optimized ODF, developed through a factorial design with HPMC and sodium starch glycolate, exhibited significantly enhanced drug release compared to the pure drug, supporting its potential as a fast-disintegrating formulation.[41]

Collectively, these findings demonstrate that solid dispersion systems can significantly improve the dissolution and oral bioavailability of ezetimibe through amorphization and molecular dispersion within hydrophilic carriers. When further integrated into patient-friendly dosage forms such as oral disintegrating films, this strategy not only enhances biopharmaceutical performance but also offers opportunities to improve patient compliance and therapeutic outcomes.

Co-Crystal

Co-crystals are crystalline solids composed of an active pharmaceutical ingredient and one or more co-formers, assembled in a well-defined stoichiometric ratio through non-covalent interactions. Forming a new crystal lattice distinct from the individual components can lead to modified physicochemical properties, most notably enhanced solubility and improved dissolution behavior, without altering the drug's molecular structure. Co-crystallization is a promising solid-state modification approach for improving the solubility and dissolution of poorly water-soluble drugs.[42] In particular, co-formers such as dicarboxylic acids (eg,

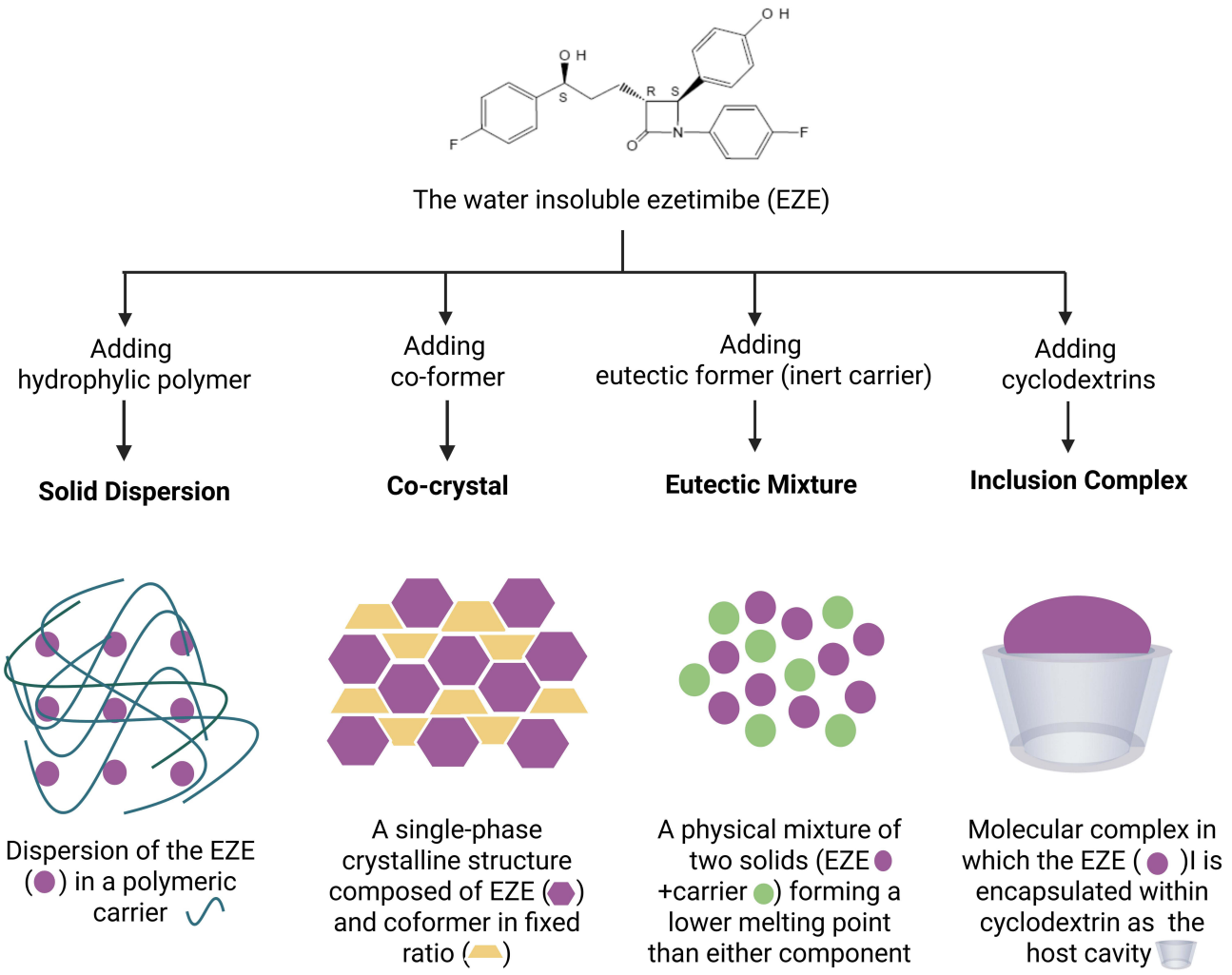

Figure 2 Ezetimibe in solid state modifications. Created in BioRender. Priani, S. (2025) https://BioRender.com/83m5ciw.

oxalic, succinic, and maleic acid) have been utilized to prepare ezetimibe cocrystals via solvent evaporation methods. These cocrystals demonstrated improved dissolution performance compared to the pure drug, with maleic acid-based cocrystals showing superior characteristics among the dicarboxylic acid series. The optimum system demonstrated an 18.8-fold increase in dissolution efficiency compared to the pure drug, with 95.2% of the drug released within 45 minutes.[25]

In another study, an ezetimibe–imidazole cocrystal was developed using a reaction crystallization method and subjected to comprehensive evaluation. This system exhibited high solubility and thermodynamic stability in water and simulated intestinal fluid. Compared to pure ezetimibe, the cocrystal exhibited significantly enhanced in vitro dissolution, with a Cmax of 5.0 µg/mL in water (vs ~3.7 µg/mL for the pure drug) and 40.0 µg/mL in FaSSIF (vs ~12.0 µg/mL), and a higher AUC (2963.62 ± 9.1 µg·min/mL). Importantly, in vivo studies confirmed its hypolipidemic efficacy, showing a significant reduction in lipid levels and an atherogenic index comparable to that of the control (normal) group, indicating its therapeutic relevance and biocompatibility.[29] Overall, co-crystallization has been demonstrated to significantly enhance the dissolution of ezetimibe, making it a promising strategy to improve the biopharmaceutical performance of ezetimibe.

Inclusion Complex

Another promising approach to improve ezetimibe's solubility and oral performance is the formation of inclusion complexes, particularly with cyclodextrins. Inclusion complexes are molecular assemblies in which a hydrophobic drug is partially or entirely encapsulated within the cavity of a host molecule, typically a cyclodextrin. This encapsulation shields the drug from the aqueous environment, increasing its apparent solubility and dissolution rate without altering its

chemical structure.[43–45] Several cyclodextrin derivatives have been investigated for the formation of inclusion complexes with ezetimibe. A study utilizing β-cyclodextrin in a 1:1 molar ratio, along with solubilizing agents such as polyethylene glycol 1000 succinate (TPGS) and L-ascorbic acid-2-glucoside (AA2G), enhanced dissolution performance. The ternary inclusion complex E–CD–AA2G significantly enhanced ezetimibe dissolution, achieving 82.5% ± 2.8% drug release at 30 minutes and a 3–3.5-fold increase in dissolution efficiency (DE) compared to the pure drug, which dissolved only 36.2% ± 4.2% over 120 minutes ($p < 0.05$ for all comparisons), and also demonstrated superior anti-dyslipidemic effects relative to both the pure drug and the control group.[46]

In a more recent investigation, inclusion complexes were prepared using various modified β-cyclodextrins, including RM-β-CD, DM-β-CD, TM-β-CD, HP-β-CD, and SBE-β-CD. All complexes, except those with SBE-β-CD, exhibited significantly improved solubility and dissolution when used in higher molar ratios. Among them, RM-β-CD and DM-β-CD showed the most notable enhancement. These findings underscore the utility of cyclodextrin-based inclusion complexes as an effective formulation strategy for ezetimibe, by improving aqueous solubility and dissolution behavior.[47]

Eutectic Mixture

Eutectic mixtures represent another solid-state modification strategy to enhance the dissolution behavior of poorly water-soluble drugs. These systems are formed by the intimate combination of two or more components that exhibit a melting point lower than the individual constituents when mixed in a particular ratio. This reduced melting point often correlates with enhanced molecular mobility and increased wettability, which can contribute to improved dissolution rates.[48]

For ezetimibe, eutectic systems have been explored using pharmaceutically acceptable co-formers such as salicylic acid, methylparaben, and nicotinamide. Among the formulations tested, eutectic mixtures of salicylic acid and methylparaben significantly enhanced drug dissolution, indicating favorable solid-state interactions that facilitated the more rapid release of the drug. In contrast, the eutectic mixture with nicotinamide resulted in a marked reduction in dissolution, suggesting that not all co-formers yield beneficial interactions. These findings underscore the significance of co-former selection in eutectic systems and confirm that properly designed eutectic mixtures can serve as a viable and straightforward approach to enhance the biopharmaceutical performance of ezetimibe, without necessitating complex processing or specialized equipment.[49] Another study developed an ezetimibe–succinimide eutectic system via mechanochemical grinding. This system demonstrated approximately a two-fold increase in solubility and dissolution rate, and markedly improved oral bioavailability.[50] These results highlight the potential of eutectic mixtures as a simple yet effective strategy to improve the dissolution and oral bioavailability of ezetimibe, provided that co-former selection is carefully optimized.

Particle Size Reduction Techniques

In addition to solid-state modifications, particle size reduction is another widely adopted strategy to improve ezetimibe's solubility and oral bioavailability. This approach aims to decrease the drug's particle size, typically to the nano- or microscale range, which significantly enhances the surface area available for dissolution as explained by the Noyes-Whitney equation. The increased surface area yields a faster dissolution rate, improved apparent, and facilitates better absorption in the gastrointestinal tract.[51,52]

Nanoparticles

Nanoparticles are submicron colloidal carriers that can encapsulate or adsorb drug molecules, enhancing their solubility, stability, and intestinal absorption through increased surface area and interaction with biological membranes.[53] Ezetimibe has been incorporated into nanoparticles to improve oral delivery. One study used polysaccharide fractions from *Linum usitatissimum* to develop ezetimibe nanoparticles via nanoprecipitation and emulsion solvent evaporation techniques. The nanoprecipitation approach yielded better dissolution performance than the emulsion-based method, demonstrating enhanced release characteristics. Nanoparticles prepared via nanoprecipitation exhibited higher ezetimibe dissolution (83.1%) compared to emulsion-based nanoparticles (80.3%) and showed improved drug release compared to the pure drug.[54]

Another study employed ionotropic gelation to formulate chitosan-based ezetimibe nanoparticles, which exhibited significantly improved dissolution compared to the marketed tablet. Nanoparticles showed higher ezetimibe release than the marketed tablet, with 35.2% vs 10.95% at 30 minutes and 66.8% vs 38.2% total release ($p < 0.05$). Moreover, this

formulation demonstrated superior antihyperlipidemic effects in vivo, effectively reducing total cholesterol, triglycerides, LDL-C, VLDL-C, and atherogenic index compared to untreated and marketed product groups. These findings highlight the potential of nanoparticle systems to improve both the biopharmaceutical and therapeutic performance of ezetimibe.[55]

Nanocrystal

Nanocrystals are submicron-sized crystalline particles composed entirely of the active drug. They offer a carrier-free approach suitable for hydrophobic compounds. By reducing particle size, nanocrystals improve surface area and dissolution rate. Surfactants or stabilizers are commonly used to stabilize the crystalline dispersions.[56,57] In the case of ezetimibe, nanocrystals were successfully developed using a bottom-up precipitation method with stabilizers like d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) and L-ascorbic acid-2-glucoside (AA2G). Both stabilizers enhanced solubility and dissolution. TPGS-stabilized nanocrystals showed superior pharmacodynamic effects in vivo. This enhancement is partially attributed to TPGS's P-gp inhibitor function. P-gp is an efflux transporter expressed in intestinal epithelial cells that can limit the oral absorption of certain drugs.[58] By inhibiting P-gp, TPGS helps to reduce drug efflux back into the intestinal lumen, allowing for greater intracellular concentration and systemic absorption. Therefore, TPGS's dual role as both a stabilizer and P-gp inhibitor makes it particularly valuable in nanocrystal formulations aimed at improving the oral bioavailability of ezetimibe.[24]

Fibrous Microparticle

Fibrous microparticles are submicron-sized drug-loaded fibers typically produced via techniques such as electrospray or electrospinning. These structures increase the drug's surface area and promote rapid dissolution by dispersing the active pharmaceutical ingredient in a hydrophilic carrier matrix.[59] In one study, electrosprayed fibrous microparticles composed of ezetimibe, polyvinylpyrrolidone (PVP), and Cremophor RH40 significantly enhanced both solubility and dissolution performance compared to the pure drug. Among the tested formulations, the one containing ezetimibe, PVP, and Cremophor RH40 at a 1:5:0.1 weight ratio demonstrated the most favorable performance in terms of aqueous solubility and dissolution rate. The system showed significantly enhanced solubility and dissolution (~26-fold and ~4.5-fold, respectively) compared to pure drug. Pharmacokinetic evaluation further confirmed a significant enhancement in oral bioavailability, as evidenced by increased systemic exposure. These findings support the potential of fibrous microparticles as a promising delivery platform for poorly water-soluble drugs such as ezetimibe.[60]

Lipid/Surfactant-Based Formulations

Another formulation strategy involves lipid/surfactant-based systems, which aim to improve ezetimibe's solubilization and intestinal absorption. Ezetimibe is a BCS Class II drug with limited aqueous solubility. These systems form colloidal dispersions or emulsions in the gastrointestinal tract, enhancing dissolution and promoting lymphatic uptake.[61] Lipid-based carriers, particularly those containing specific surfactants that can modulate intestinal efflux mechanisms such as P-glycoprotein (P-gp), potentially increase intracellular drug concentrations by inhibiting drug efflux.[62] Some lipid-based systems, employing long-chain triglycerides, may promote lymphatic transport, thereby partially bypassing hepatic first-pass metabolism. The combined ability to increase solubility, sustain supersaturation, promote lymphatic uptake, and inhibit efflux mechanisms makes lipid/surfactant-based delivery particularly effective for enhancing the oral bioavailability of ezetimibe. In lipid-based delivery systems, ezetimibe has been successfully developed using various platforms, including microemulsions, self-nanoemulsifying drug delivery systems (SNEDDS), nanostructured lipid carriers (NLCs), solid lipid nanoparticles (SLNs), and micellar systems. Figure 3 illustrates the low aqueous solubility of ezetimibe and its incorporation into various lipid- and surfactant-based delivery systems.

Microemulsion

Microemulsion systems represent another promising strategy to enhance ezetimibe's solubility and oral bioavailability. Microemulsions are thermodynamically stable, isotropic dispersions composed of oil, surfactant, cosurfactant, and aqueous phase. Due to their nanometric droplet size and high interfacial surface area, they significantly improve drug solubilization and facilitate diffusion across biological membranes. The spontaneous formation and thermodynamic stability of microemulsions facilitate rapid dispersion in gastrointestinal fluids, thereby enhancing the rate and extent of

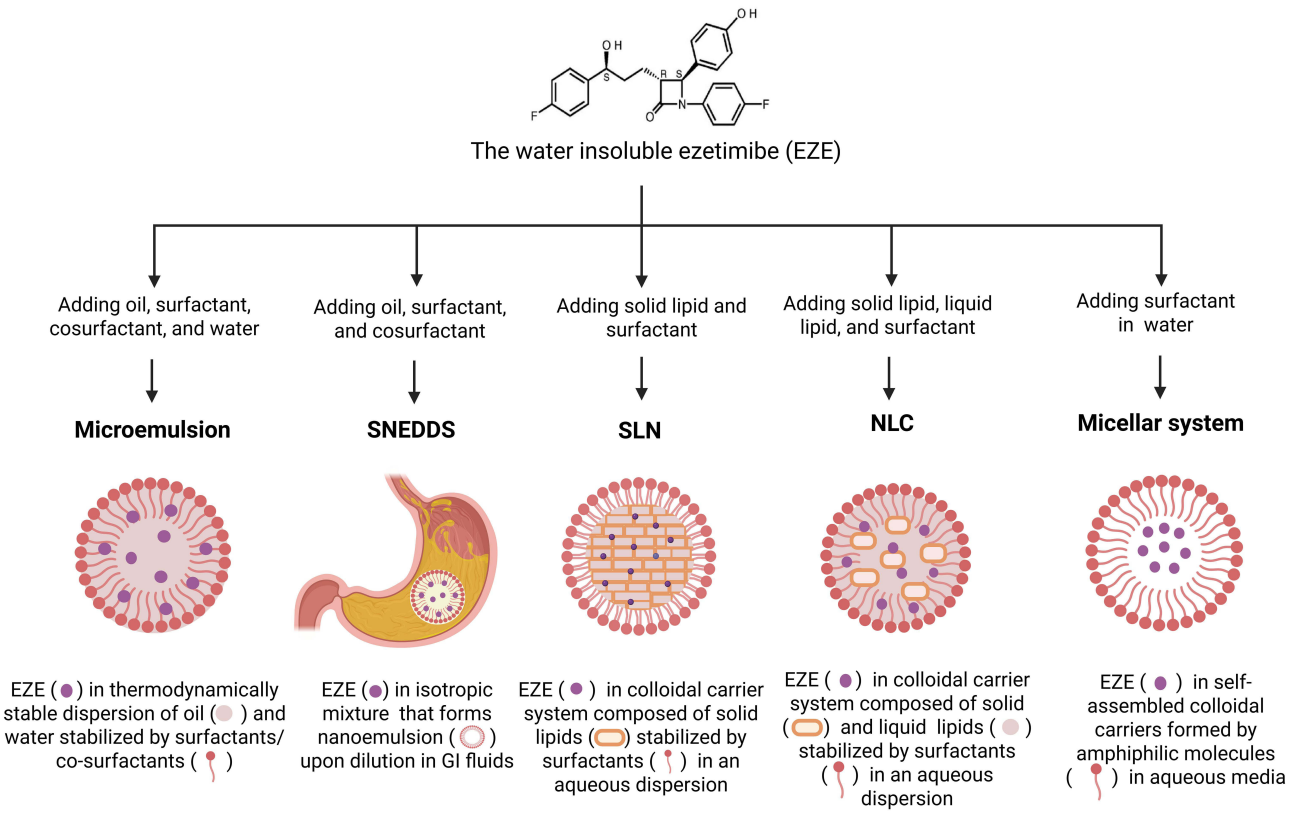

Figure 3 Ezetimibe in surfactant/lipid-based formulations. Created in BioRender. Priani, S. (2025) https://BioRender.com/2z72asq.

drug dissolution.[63] A notable example is the development of nano-ezetimibe from a volatile o/w microemulsion system, which contains ethyl acetate as the oil phase, Brij 35 as the surfactant, and ethanol as the cosurfactant. This formulation demonstrated a markedly enhanced dissolution rate compared to the pure drug, underscoring the potential of micro-emulsion-based approaches in addressing ezetimibe's solubility limitations. Nano-ezetimibe exhibited a significantly improved dissolution rate, reaching 98.11% in 30 minutes, compared to 5.17% and 7.67% for the pure drug in water and a surfactant medium, respectively.[64] These findings suggest that microemulsion-based systems provide a viable approach to enhancing the dissolution and oral bioavailability of ezetimibe, particularly in overcoming its poor aqueous solubility.

Self-Nanoemulsifying Drug Delivery System (SNEDDS)

SNEDDS represent a promising lipid-based strategy to enhance the oral delivery of poorly water-soluble drugs. These systems are isotropic mixtures of oil, surfactant, and co-surfactant that spontaneously form fine oil-in-water nanoemulsions upon mild agitation in gastrointestinal fluids. The resulting nano-sized droplets markedly increase the drug's surface area, maintain it in a solubilized state, and facilitate its absorption. Moreover, the surfactant components may inhibit intestinal P-glycoprotein (P-gp) efflux, further enhancing systemic exposure.[65,66] Recent studies have demonstrated the effectiveness of SNEDDS in improving the bioavailability of ezetimibe. An optimized SNEDDS formulation, developed using a Box–Behnken Design, incorporated Peceol as the oil phase, Tween 80 as the surfactant, and Transcutol-P as the co-surfactant. This formulation demonstrated a significant improvement in drug release compared to the pure drug, confirming the benefits of statistical design in achieving optimal performance (49.21% after 5 minutes; 95.27% after 40 minutes).[67]

Another study developed a solid SNEDDS system containing Capryol 90 and Cremophor EL, demonstrating superior solubility and dissolution behavior in a separate investigation. Solid SNEDDS enhanced aqueous solubility (~337 µg/mL vs 1.69 µg/mL) and improved drug dissolution 2–3-fold compared to pure drug (~60% vs ~25% at 30 min). Pharmacokinetic studies revealed a substantial increase in plasma concentration and overall systemic exposure compared to the pure drug.

These findings highlight the dual advantage of SNEDDS in enhancing both the solubilization and intestinal absorption of ezetimibe, making it a compelling approach for the oral delivery of this BCS Class II compound.[39]

Solid Lipid Nanoparticles (SLNs)

Another promising lipid-based formulation strategy is solid lipid nanoparticles (SLNs), which have been extensively explored to enhance the solubility and oral bioavailability of poorly water-soluble drugs. SLNs consist of solid lipid cores that encapsulate the drug and are stabilized by surfactants, forming nanoscale particles that remain stable in the gastrointestinal environment. This system increases the dissolution rate, may prolong gastrointestinal residence time, and protects the drug from enzymatic or chemical degradation.[68,69] In one study, ezetimibe-loaded SLNs were developed using high-pressure homogenization, employing Compritol 88 as the solid lipid and Tween 80 as the surfactant. The resulting formulation exhibited significantly improved drug release compared to conventional suspension and marketed products. The SLN system showed an 80.2% release in 12 hours, ~6 times higher than the suspension and 2 times higher than the marketed product ($p < 0.05$). Furthermore, pharmacokinetic analysis demonstrated a notable increase in peak plasma concentration and overall drug exposure. These findings highlight the potential of SLNs as an effective carrier system to enhance ezetimibe's oral delivery and therapeutic performance.[26]

Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers (NLCs) are advanced lipid-based delivery systems composed of solid and liquid lipids, stabilized by surfactants. Unlike SLNs, NLCs incorporate a certain proportion of liquid lipids into the solid lipid matrix, resulting in a less ordered internal structure. This structural imperfection provides additional space to accommodate drug molecules, resulting in a higher drug loading capacity and reduced drug expulsion during storage. The lipid matrix protects the encapsulated drug from degradation, enhancing its solubility and dissolution rate. Additionally, by promoting lymphatic uptake and potentially bypassing hepatic first-pass metabolism, NLCs improve the oral bioavailability of poorly water-soluble drugs.[70–72] Several studies have explored various formulation approaches and processing techniques, yielding consistently favorable outcomes in terms of ezetimibe's dissolution and therapeutic performance.

One notable approach employed ultrasonication to develop NLCs of ezetimibe using a lipid blend of oleic acid and stearic acid, stabilized with Tween 80 and poloxamer 188. Adjusting the solid-to-liquid lipid ratio allowed modulation of the drug release profile (drug release ranged from 43.5 ± 3.8 to 79.4 ± 2.12% at the end of the 24 h). In hyperlipidemic animal models, the optimized formulation significantly outperformed ezetimibe suspension by effectively reducing total cholesterol, triglycerides, and LDL levels while enhancing HDL levels, suggesting improved efficacy.[17] In a separate strategy, the high-pressure homogenization technique was used to fabricate NLCs composed of Capmul PG8 and glycerol monostearate as the lipid matrix, with poloxamer 188 as a stabilizer. This system displayed a biphasic release pattern (an initial burst followed by a sustained phase) ideal for maintaining prolonged therapeutic levels. In vivo results confirmed superior lipid profile normalization compared to the pure drug, highlighting its potential in long-term lipid management.[28]

Another study employed a microemulsion-based method, combining Monosteol and Capryol 90 with a surfactant mixture of Kolliphor EL and Transcutol HP. The resulting NLCs exhibited rapid dispersion and nearly complete drug release within minutes. Pharmacokinetic evaluation revealed enhanced systemic exposure and more pronounced cholesterol-lowering effects compared to the marketed tablet and drug suspension, underscoring the efficacy of microemulsion-templated NLCs.[73]

Further advancing this platform, one study developed NLC-loaded oral tablets by incorporating lyophilized ezetimibe-NLCs into a fast-disintegrating solid dosage form. Using response surface methodology, the formulation was optimized for disintegration time and drug release efficiency. The final tablet exhibited rapid release and disintegration (98 ± 3.09% of the drug was released at 24 h). It achieved superior bioavailability compared to a commercial ezetimibe product, demonstrating that NLCs can be effectively translated into oral forms without compromising performance.[74]

Overall, nanostructured lipid carriers have emerged as one of the most extensively explored delivery systems for ezetimibe, alongside solid dispersions. Their ability to enhance solubility, protect the drug from degradation, and promote lymphatic transport has translated into consistent improvements in dissolution, systemic exposure, and lipid-lowering efficacy across multiple studies. Furthermore, their successful incorporation into various oral dosage forms demonstrates their versatility and potential for clinical translation in improving the biopharmaceutical performance of ezetimibe.

Micellar System

Micellar systems represent a promising strategy for enhancing the solubility of poorly water-soluble drugs. These systems typically comprise amphiphilic surfactants that self-assemble in aqueous media into nanosized colloidal structures (micelles) with a hydrophobic core capable of incorporating lipophilic drugs and a hydrophilic shell that ensures dispersion stability.[75] The study developed micellar formulations of ezetimibe using Kolliphor® RH40 as the surfactant and croscarmellose as a hydrophilic carrier. Two formulations were compared: MS-I (drug-to-surfactant ratio 1:0.25) and MS-II (1:0.75). The MS-II formulation demonstrated superior dissolution performance, with approximately a 2.48-fold enhancement compared to the pure drug, higher than that of the solid dispersion (2.16-fold) and the MS-I formulation (~1.24-fold). In vivo evaluation further confirmed the enhanced performance of MS-II, which showed significantly higher Cmax and AUC values, as well as a faster Tmax, indicating improved absorption and bioavailability.[76]

In another study, self-micellizing solid dispersions of ezetimibe were prepared using the same surfactant-polymer system. The optimized formulation exhibited approximately 2.8- to 3-fold improvement in dissolution compared to the physical mixture and pure drug. In a hyperlipidemic rat model, the micellar system significantly improved the lipid profile, reducing total cholesterol, triglycerides, and LDL cholesterol while increasing HDL levels compared to untreated groups and the pure drug. These findings suggest micellar systems provide a simple yet effective approach to enhance ezetimibe's solubility, absorption, and therapeutic efficacy through nanoscale surfactant-based delivery.[77]

Formulation Approaches to Enhance the Solubility of Ezetimibe in Combination Systems

Clinical trials have consistently demonstrated the synergistic effects of combining ezetimibe with other lipid-lowering agents. These findings have stimulated extensive research into developing formulation strategies to deliver ezetimibe in fixed-dose combinations (FDCs). While FDCs have long been utilized in the management of hypertension and diabetes mellitus, their application in dyslipidemia therapy is gaining increasing attention. The development of FDCs is primarily intended to enhance therapeutic efficacy, minimize adverse effects, and improve patient adherence by reducing pill burden.[78] For optimal dyslipidemia management, FDCs should ideally combine agents with complementary mechanisms of action to achieve additive or synergistic anti-hyperlipidemic effects. These agents must be compatible with the dosing regimen and administration schedule.[22]

Several fixed-dose combinations (FDCs) in tablet dosage form containing ezetimibe are now widely available in various strengths, particularly those combined with statins such as simvastatin, atorvastatin, rosuvastatin, and pitavastatin, as well as with bempedoic acid. Figure 4 illustrates FDC products containing ezetimibe that are currently available on the market. These combinations are specifically designed to deliver superior lipid-lowering effects by targeting different but complementary mechanisms of action.[79] Ezetimibe works by selectively inhibiting the Niemann–Pick C1-Like1 (NPC1L1) transporter in the small intestine, thereby blocking the absorption of dietary and biliary cholesterol.[80,81] In contrast, statins act at the hepatic level by inhibiting HMG-CoA reductase, a key enzyme in the endogenous cholesterol biosynthesis pathway.[82] Bempedoic acid introduces an additional mechanism by inhibiting ATP-citrate lyase, which acts upstream of HMG-CoA reductase. This allows bempedoic acid to reduce hepatic cholesterol synthesis without the typical muscle-related side effects of statins.[83,84] The mechanisms of action of ezetimibe, statins, and bempedoic acid are illustrated in Figure 5.

The rationale behind combining ezetimibe with statins or bempedoic acid lies in their complementary actions. While ezetimibe reduces cholesterol input from the intestine, statins and bempedoic acid decrease endogenous cholesterol production in the liver. Together, these dual-target approaches synergize to lower LDL cholesterol levels more effectively than monotherapy.[83,85–87] Moreover, the availability of these agents in FDCs enhances patient adherence by reducing pill burden and simplifying dosing regimens. Importantly, they also enable effective lipid control with potentially lower statin doses, which can benefit patients who are intolerant to high-dose statin therapy.[88,89] Ultimately, these combination therapies contribute to more effective long-term management of dyslipidemia and reduce the risk of atherosclerotic cardiovascular disease, especially in high-risk populations. Given the physicochemical limitations of many lipid-lowering agents, multiple studies have also explored innovative formulation strategies to enhance their solubility, stability, and

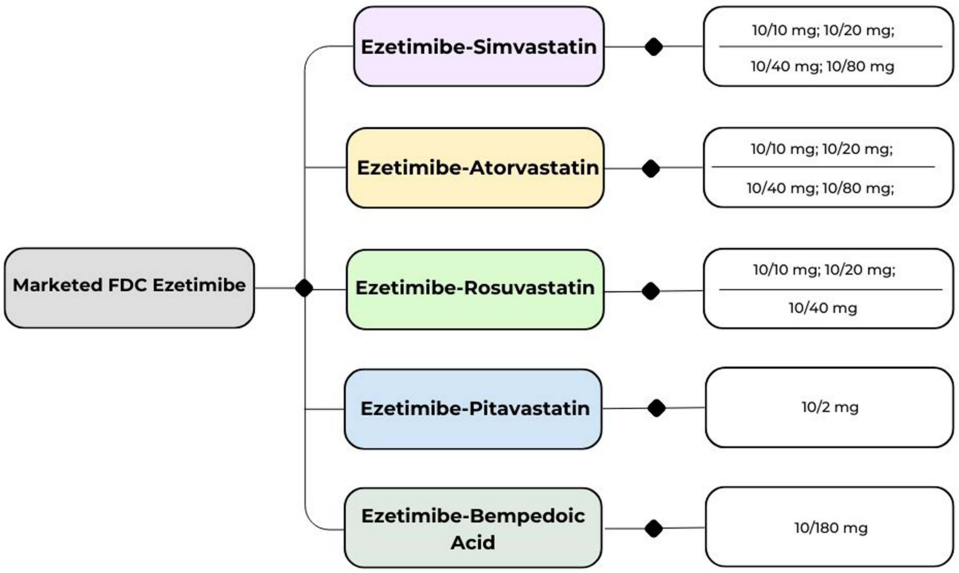

Figure 4 Marketed FDC of ezetimibe.

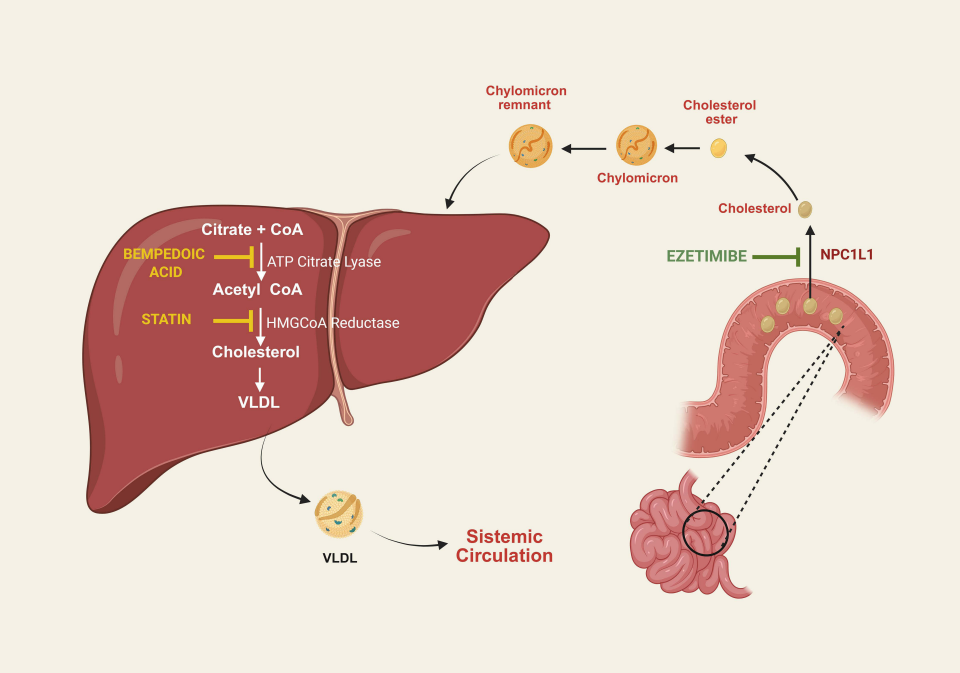

Figure 5 Mechanism of action of ezetimibe, statin, and bempedoic acid. Created in BioRender. Priani, S. (2025) https://BioRender.com/b4nunok.

bioavailability, thereby improving pharmacological performance. Numerous methods have been developed to create advanced formulations for ezetimibe–statins combinations. However, for the ezetimibe–bempedoic acid combination, no publications to date have reported alternative formulation strategies beyond the conventional tablet dosage form currently available on the market.

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Dissolution Enhancement for the Combination of Ezetimibe and Simvastatin

The effectiveness of simvastatin–ezetimibe combination therapy has been extensively demonstrated in many clinical trials.[90] A notable example is the IMPROVE-IT trial, a large-scale randomized controlled study involving 18,144 patients with acute coronary syndrome. This trial compared the efficacy of simvastatin 40 mg plus ezetimibe 10 mg with simvastatin 40 mg monotherapy. Results showed that the combination therapy significantly reduced LDL-C levels, compared to the monotherapy group ($P < 0.001$), thereby confirming the added benefit of ezetimibe in lipid-lowering therapy. These findings provided strong clinical justification for developing FDC products containing ezetimibe and simvastatin to optimize therapeutic outcomes.[91]

Numerous formulation strategies have been employed to enhance the dissolution and oral bioavailability of the combination of ezetimibe and simvastatin, both of which are classified as BCS Class II compounds with poor aqueous solubility. The study involves a 1:1 co-amorphous dispersion obtained by melt-quenching. A co-amorphous system is a homogeneous amorphous mixture composed of a drug and a low molecular weight co-former (which may be another drug or a small excipient), designed to enhance the solubility, dissolution rate, and physical stability of poorly water-soluble drugs.[92] By trapping the two drugs in a single, high-energy amorphous matrix, the formulation enhanced in vitro release by 1.50-fold for ezetimibe and 1.41-fold for simvastatin compared to the physical mixture (PM). Translation to in vivo studies confirmed pharmacokinetic and pharmacodynamic benefits, including improvements in Cmax, AUC, and serum cholesterol and triglyceride levels.[93] In a separate investigation, the solid dispersion of simvastatin and ezetimibe was prepared using the co-grinding method and evaluated across a range of weight fractions. Thermal and structural analyses (DSC, XRPD) revealed the formation of a simple eutectic phase system, while FTIR studies indicated minimal specific molecular interactions. Despite this, all tested solid dispersions showed marked improvement in ezetimibe dissolution, particularly when simvastatin content approached the eutectic composition. This enhancement allows for potential dose reduction of ezetimibe in fixed-dose combinations.[94]

A complementary strategy relies on spray-dried dual-drug nanocrystals loaded with nano-embedded microparticles (DNEM). Here, nanocrystals of both agents are precipitated into a mannitol matrix (drug-to-mannitol ratio of 3:7 w/w) and stabilized with 0.1% w/v TPGS. Shrinking the particle size into the nanometer regime produces a pronounced surface-area gain, translating into 1.65-fold and 1.45-fold increases in dissolution rate for ezetimibe and simvastatin, respectively, compared with the PM.[95] Lipid-based encapsulation has also been explored through the use of solid lipid nanoparticles prepared with glyceryl monostearate (GMS) as the lipid core and Poloxamer 188 as the surfactant, utilizing high-speed homogenization. Under dissolution testing, the resulting particles released 77.11% of ezetimibe and 74.13% of simvastatin, confirming that lipid matrices can effectively accommodate and liberate both drugs, despite their hydrophobicity.[96]

Overall, various formulation strategies, including co-amorphous dispersions, eutectic systems, nanocrystals, and lipid-based carriers, have shown potential to improve the dissolution and biopharmaceutical performance of the combination of ezetimibe and simvastatin. While in vitro and preclinical findings are promising, further studies are needed to confirm their clinical relevance and to support the development of fixed-dose combination products with optimized therapeutic outcomes and improved patient adherence.

Dissolution Enhancement for the Combination of Ezetimibe and Atorvastatin

Similar to the simvastatin–ezetimibe combination, numerous clinical studies have also investigated the synergistic potential of combining ezetimibe with atorvastatin.[97] A meta-analysis of 14 clinical trials involving 3,105 subjects demonstrated that combining atorvastatin with ezetimibe 10 mg was significantly more effective than doubling the dose of atorvastatin monotherapy. The combination reduced LDL-C by 14.16%, non-HDL-C by 14.01%, total cholesterol (TC) by 11.06%, and triglycerides (TG) by 5.95%, showing a statistically significant improvement over high-dose atorvastatin alone ($p < 0.001$). These findings highlight the added therapeutic value of ezetimibe in lipid-lowering therapy, particularly in cases where statin monotherapy is insufficient or dose escalation is limited by tolerability.[98]

Formulation strategies for the FDC of ezetimibe and atorvastatin have been extensively explored to address their poor aqueous solubility and to enhance overall therapeutic efficacy. Both active pharmaceutical ingredients are classified as

BCS II compounds, characterized by low solubility but high permeability.[99] Several advanced drug delivery systems have been developed to overcome these challenges, including solid dispersions, SMEDDS, SNEDDS, and modified-release bilayer tablets. These approaches aim to enhance the dissolution rate, thereby improving oral bioavailability and ultimately contributing to better therapeutic outcomes in the management of dyslipidemia.

Ezetimibe and atorvastatin have also been formulated as a solid dispersion system using solvent evaporation, with polyvinylpyrrolidone K30 (PVP K30) as a hydrophilic polymeric carrier. This formulation markedly improved the dissolution profiles of both drugs compared to their binary physical mixture, with the solid dispersion achieving 100% release of atorvastatin and 90% of ezetimibe, in contrast to only 75% and 47.8%, respectively, observed in the binary mixture. Moreover, in vivo studies demonstrated enhanced lipid-lowering effects, suggesting improved systemic absorption and increased therapeutic potential.[100]

Another formulation approach involves the development of SMEDDS (self-microemulsifying drug delivery system), which was prepared using ethyl oleate as the oil phase, Tween 80 as the surfactant, and PEG 600 as the co-surfactant. This system enabled rapid and uniform dissolution of both ezetimibe and atorvastatin across various media, indicating enhanced solubilization capacity.[101] In a more comprehensive study, the combination of ezetimibe and atorvastatin was also formulated into SNEDDS using Capryol 90 as the oil, a mixture of Tween 80 and Kolliphor RH40 as surfactants, and Transcutol HP as the co-surfactant. In vitro evaluation showed a remarkable increase in drug release, exceeding 99% for both drugs, compared to less than 8% for the pure drug suspension. In vivo studies further confirmed a significant enhancement in bioavailability, with Cmax values for atorvastatin and ezetimibe increasing by 2.22- and 2.33-fold, respectively, and AUC values rising by 3.55- and 3.77-fold, compared to a conventional suspension. Additionally, the SNEDDS formulation demonstrated superior lipid-lowering efficacy, particularly in reducing total cholesterol and non-HDL-C levels.[27]

Another strategy involved a multiparticulate system combining ezetimibe micellar formulations with atorvastatin solid dispersions using Kolliphor RH40 and croscarmellose. In in vitro studies, this system demonstrated rapid drug release, attributed to reduced crystallinity and enhanced solubilization, with ezetimibe and atorvastatin showing significantly faster dissolution than their raw forms. In diabetic hyperlipidemic rats, low and high doses reduced cholesterol, triglycerides, lipoproteins, ALT, and AST levels. Notably, the low-dose system (2 and 6.7 mg/kg) achieved comparable lipid-lowering and hepatoprotective effects to those of the high-dose raw drugs, highlighting the formulation's efficiency in improving bioavailability and therapeutic outcomes while minimizing dose requirements.[102]

In another approach, a modified-release bilayer tablet was developed using HPMC K-100 as the rate-controlling polymer. The formulation consisted of an immediate-release (IR) layer for atorvastatin and a sustained-release (SR) layer for ezetimibe, with the release design tailored to the distinct pharmacological roles of each drug. Atorvastatin requires rapid systemic absorption to effectively inhibit hepatic cholesterol synthesis, whereas ezetimibe benefits from prolonged intestinal residence to block cholesterol absorption continuously. The bilayer system achieved the desired release profile, with the IR layer releasing 96% of atorvastatin within 2 hours, and the SR layer releasing 80% of ezetimibe over 24 hours. This dual-release strategy resulted in improved therapeutic outcomes for preventing and treating hyperlipidemia.[103]

The combination of ezetimibe and atorvastatin has been the most widely explored among ezetimibe-based fixed-dose formulations. Various formulation approaches, including solid dispersions, lipid-based systems, and modified-release dosage forms, have consistently demonstrated improvements in dissolution, bioavailability, and lipid-lowering efficacy. These outcomes suggest that further development of this combination holds promise for optimizing therapeutic strategies, particularly in patients requiring comprehensive lipid management beyond statin monotherapy.

Dissolution Enhancement for the Combination of Ezetimibe and Rosuvastatin

Despite rosuvastatin being categorized as a high-intensity statin with high potency and relatively better aqueous solubility than other statins, several clinical studies have demonstrated the added benefit of combining it with ezetimibe.[104] One notable example is the RACING trial, which involved 3780 patients with ASCVD. The study compared the efficacy of a moderate-dose combination (rosuvastatin 10 mg plus ezetimibe 10 mg) with that of high-dose rosuvastatin monotherapy (20 mg daily). The results showed that the combination was non-inferior in terms of 3-year composite cardiovascular outcomes, while achieving a higher proportion of patients reaching LDL-C targets and demonstrating lower rates of statin intolerance-related discontinuation or dose reduction.[105]

However, the number of formulation-based studies on this combination remains relatively limited. This may be due to rosuvastatin's inherently higher solubility and pharmacological potency, which reduce the perceived need for advanced formulation interventions. Nonetheless, recent research has begun to explore innovative delivery platforms to optimize further the bioavailability and therapeutic efficacy of the rosuvastatin–ezetimibe combination. One approach employed PLGA nanoparticles stabilized with Pluronic F-127, prepared via nanoprecipitation. The formulation provided a sustained drug release exceeding 90% over 24 hours. The formulation provided a sustained drug release exceeding 90% over 24 hours and significantly improved the pharmacokinetic profile in vivo, with increased AUC and Cmax for both ezetimibe and rosuvastatin compared to a conventional suspension.[106] In summary, although formulation-based studies on the rosuvastatin and ezetimibe combination are still limited, emerging strategies have shown potential to enhance its pharmacokinetic performance and support its therapeutic value.

Dissolution Enhancement for the Combination of Ezetimibe and Lovastatin

The combination of ezetimibe and lovastatin has also been explored, although research in this area remains limited. The two main formulation strategies investigated are solid dispersion and co-amorphous systems. The solid dispersion was prepared by spray drying using Soluplus® (75%) as the polymeric carrier. This approach resulted in a substantial increase in the dissolution rates of both drugs, particularly ezetimibe, indicating improved solubility through polymer-mediated dispersion. However, the observed in vitro enhancement still requires further in vivo validation to confirm its therapeutic relevance. In contrast, the co-amorphous system, developed via quench cooling, did not improve the dissolution rates of either drug. This outcome may be attributed to insufficient intermolecular interactions or inadequate stabilization of the amorphous phase for this drug combination. These findings indicate that solid dispersion using Soluplus® is a more promising strategy for the combination than co-amorphization in enhancing dissolution performance. However, further studies are needed to evaluate its biopharmaceutical effectiveness.[107,108] Overall, while preliminary findings suggest that solid dispersion may offer advantages for the ezetimibe and lovastatin combination, further investigation is necessary to establish its biopharmaceutical and clinical potential.

Pharmacokinetic Modulation Through Formulation Strategies

Various formulation strategies have been employed to enhance the dissolution of ezetimibe, either as a single agent or in combination therapies. Techniques such as solid-state modification, particle size reduction, and lipid/surfactant-based delivery systems have demonstrated considerable success in improving its dissolution behavior. The effectiveness of these approaches is highly dependent on appropriate formulation design, including the selection of excipients, their proportions, and the manufacturing methods utilized. Enhanced dissolution is generally associated with improved oral bioavailability, particularly for drugs with low aqueous solubility, such as ezetimibe. This is because increased dissolution can lead to a higher concentration gradient across the intestinal membrane, thereby facilitating absorption. However, this relationship is not always straightforward. Several physiological and biopharmaceutical factors may influence in vivo drug performance, potentially leading to inconsistencies between in vitro and in vivo outcomes. Therefore, although in vitro dissolution testing provides valuable preliminary data, it is not a sufficient predictor of bioavailability. In vivo studies remain essential to confirm the pharmacokinetic advantages of the developed formulations. Variations may occur due to factors such as gastrointestinal pH variability, enzymatic activity, drug precipitation upon dilution, and first-pass metabolism, all of which can significantly impact systemic drug exposure and are not fully captured by in vitro models.

Table 1 summarizes the impact of formulation strategies on the pharmacokinetic profile of ezetimibe compared to pure drug suspensions or marketed tablet formulations. In general, it can be observed that formulation modifications consistently enhance bioavailability, as indicated by increases in both AUC and Cmax values. This improvement can be attributed to enhanced dissolution rates, improved solubility, and, in some cases, increased permeability resulting from the presence of surfactants or nanosizing techniques. Additionally, specific delivery systems may bypass or reduce the extent of first-pass metabolism, thereby increasing systemic drug exposure.

An increase in systemic exposure is commonly assessed through the measurement of relative bioavailability, which reflects the extent of drug absorption from a test formulation compared to a reference, such as a pure drug suspension or a marketed product. In the case of ezetimibe, various formulation strategies have demonstrated a wide range of relative

Table 1 Effect of Formulation Development on the Pharmacokinetic Profile of Ezetimibe

Formulation System (Reference)	Pharmakokinetic Parameters		Relative Bioavailability
	Comparator	Advanced Formulation	
Ezetimibe in surface-modified solid dispersions (SMSD) and solvent-evaporated solid dispersions (SESD)[39]	**Pure drug**: - AUC:3.14±0.69 h.µg/mL - Cmax: 0.30±0.26 µg/mL - Tmax:1.40±0.92 h	**SMSD**: - AUC:4.96±0.73 h.µg/mL - Cmax:0.46±0.18 µg/mL - Tmax:0.75±0.42 h **SESD:** - AUC:5.58±1.25 h.µg/mL - Cmax:0.98±0.46 µg/mL - Tmax: 0.83±0.25 h	SMSD: 157.96% SESD: 177.70%
Ezetimibe in a binary and ternary solid dispersion system[40]	**Pure drug**: - AUC:3.14±0.69 h.µg/mL - Cmax: 0.30±0.26 µg/mL - Tmax:1.40±0.92 h	**Binary system (BS):** - AUC:4.91±10.50 h.µg/mL - Cmax:0.53±0.12 µg/mL - Tmax:0.66±0.28 h **Ternary system (TS)**: - AUC:5.44±0.21 h.µg/mL - Cmax:0.86±0.13 µg/mL - Tmax: 1.16±0.28 h	BS: 156,50% TS: 173,25%
Ezetimibe in eutectic mixture system[50]	**Pure drug:** AUC: 8.98 ± 0.36 ng.h/mL	**Eutectic mixture**: AUC:28.03 ± 2.22 ng.h/mL	312.14%
Ezetimibe in fibrous nanoparticles[60]	**Pure drug:** - AUC: 3.01 ± 0.55 h.µg/mL - Cmax: 0.28 ± 0.11 µg/mL - Tmax: 1.38 ± 0.85 h	**Fibrous microparticle:** - AUC: 6.21 ± 0.24 h.µg/mL - Cmax: 0.73 ± 0.21 µg/mL - Tmax: 1.24 ± 0.35 h	206.31%
Ezetimibe in SNEDDS[39]	**Pure drug:** - AUC: 3.14±0.69 h.µg/mL - Cmax: 0.30±0.26 µg/mL - Tmax: 1.40±0.9 h	**S-SNEDDS**: - AUC: 5.05±0.90 h.µg/mL - Cmax: 0.62±0.31 µg/mL - Tmax: 1.25±0.41 h	160.82%
Ezetimibe in SLN[26]	**Suspension**: - AUC: 13.21±2.91 h.µg/mL - Cmax: 0.39±0.74 µg/mL - Tmax: 1.43±0.20 h **Marketed product**: - AUC: 34.57±8.75 h.µg/mL - Cmax: 2.83±0.74 µg/mL - Tmax: 1.65±0.20 h	**SLN:** - AUC:114.48±21.53 h.µg/mL - Cmax: 6.32±1.87 µg/mL - Tmax:1.83±0.51 h	Suspension: 866.62% Marketed: 331.15%

(*Continued*)

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Table 1 (Continued).

Formulation System (Reference)	Pharmakokinetic Parameters		Relative Bioavailability
	Comparator	**Advanced Formulation**	
Ezetimibe in NLC[73]	**Suspension:** - AUC: 312.01±62.51 h.µg/mL - Cmax: 33.69±5.12 µg/mL - Tmax: 2 h **Marketed product:** - AUC: 516.15±98.13h.µg/mL - Cmax: 52.49±4.43 µg/mL - Tmax: 1.65±0.20 h	**NLC:** - AUC: 1273.38±154.77 h.µg/mL - Cmax: 85.74±6.31 - Tmax: 1 h	Suspension: 408.12% Marketed: 246.70%
Ezetimibe in NLC (tablet)[74]	**Marketed tablet (Ezetrol©)** - AUC: 15.36 ± 0.86 ng.h/mL - Cmax:2.79 ± 0.15 ng/mL - Tmax: 1.5 ± 0 h	**NLC** - AUC: 22.44 ± 2.68 ng.h/mL - Cmax: 3.57 ± 0.27 ng/mL - Tmax: 1.5 ± 0 h	146,09%
Ezetimibe in miccelar system[76,77]	**Pure drug**: - AUC: 253.13±17.90 ng.h/mL - Cmax: 22.13 ± 1.86 ng/mL - Tmax: 2.5 ±1.20 h	Micellar system: - AUC: 332.76±32.26 ng.h/mL - Cmax: 37.10 ± 7.88 ng/mL - Tmax: 1.50 ±1.04	131.46%
Ezetimibe and simvastatin in a co-amorphous system[93]	**Physical mixture (SIM)** - AUC: 605.26±24.76 µg/mL.h - Cmax: 91.14±11.062 µg/mL - 2.00±0 h	**Co-amorphous (SIM)** - AUC: 728.33±93.30 µg/mL.h - Cmax: 131.346±0.88 µg/mL - Tmax:2.00±0 h	120.33%
Ezetimibe and atorvastatin in SNEDDS[27]	**Pure drug in suspension:** Ezetimibe - AUC: 48.73 ±1.95 µg.h/mL - Cmax: 7.75 ±0.12 µg/mL - Tmax: 1.54 ±0.21 h Atorvastatin - AUC:59.04 ±1.07 µg.h/mL - Cmax:8.19 ±0.11 µg/mL - Tmax:1.58 ±0.33 h	**SNEDDS** Ezetimibe: - AUC:183.80 ± 2.73 µg.h/mL - Cmax:18.08 ± 0.13 µg/mL - Tmax:0.23 ± 0.01 h Atorvastatin: - AUC:209.56 ± 2.28 µg.h/mL - Cmax:18.20 ± 0.05 g/mL - Tmax:0.23 ± 0.05 h	Ezetimibe: 377,18% Atorvastatin: 354,95%
Ezetimibe and rosuvastatin in PLGA nanoparticles[106]	**Suspension:** Ezetimibe - AUC:177 ± 12.37 ng.hr/mL - Cmax: 94 ± 7.81 ng/mL Rosuvastatin: - AUC: 691.21 ± 11.81 ng.hr/mL - Cmax: 281.67 ± 11.2 ng/mL	**Nanoparticles** Ezetimibe - AUC: 438.2 ± 46.36 ng.hr/mL - Cmax: 162.4 ± 16.52 ng/mL Rosuvastatin: - AUC:1,858.64 ± 59.44 ng.hr/mL - Cmax:622.81 ± 43.76 ng/mL	Ezetimibe: 247.57% Rosuvastatin: 268.89%

Abbreviations: AUC, area under the curve; BS, binary system; Cmax, maximum plasma concentration; EZE, ezetimibe; NLC, nanostructured lipid carriers; SESD, supersaturable eutectic solid dispersion; SIM, simvastatin; SLN, solid lipid nanoparticles; SMSD, supersaturable microstructured solid dispersion; SNEDDS, self-nanoemulsifying drug delivery system; Tmax, time to reach maximum plasma concentration; TS, ternary system.

bioavailability values, from 120% up to 866% when compared to pure drug suspensions. These differences are likely attributable to variations in formulation design, excipient selection, particle size, and manufacturing techniques.

Several studies have also reported relative bioavailability values in comparison to marketed ezetimibe formulations, with notable improvements observed. One particularly significant example is the use of solid lipid nanoparticles, which achieved a relative bioavailability of 866.62% compared to the pure drug suspension and 331.15% compared to the marketed product. In this formulation, compritol (as the lipid matrix) and Tween 80 (as the surfactant) were employed, and the SLN were produced using high-pressure homogenization. The substantial enhancement in bioavailability is believed to result from multiple contributing factors, including reduction in particle size to the nanometer range, transformation of the crystalline drug into an amorphous form, and improved solubilization of ezetimibe within the lipid matrix.[26] Moreover, SLNs have also been reported to inhibit P-gp efflux activity, thereby further enhancing drug retention and absorption in the intestinal epithelium. This is particularly relevant for ezetimibe, whose oral bioavailability is partly limited by P-gp-mediated efflux.[109]

A significant enhancement in the pharmacokinetic profile of ezetimibe was achieved through the development of a nanostructured lipid carrier (NLC) system formulated using Monosteol (propylene glycol monopalmitostearate, a long-chain lipid), Capryol 90, Kolliphor EL, and Transcutol HP. The NLC demonstrated relative bioavailability values of 408.01% and 246.70% compared to the pure drug suspension and marketed product, respectively. This improvement is attributed to enhanced drug solubilization, lymphatic transport promoted by long-chain lipids, P-glycoprotein efflux inhibition by Kolliphor® EL, and the permeation-enhancing properties of Transcutol® HP. These results confirm the NLC system's potential in significantly improving the systemic exposure of ezetimibe.[73]

In addition to the increased AUC and Cmax observed across various ezetimibe formulation strategies, several studies have consistently demonstrated a reduction in Tmax, indicating a faster onset of systemic absorption. This decrease in Tmax has been reported in solid dispersions, fibrous microparticles, nanoparticles, NLCs, and SNEDDS-based formulations. A shortened Tmax reflects enhanced dissolution and absorption rates, which are often the result of improved physicochemical properties of the drug achieved through formulation modification. For example, in nanoparticle and microparticle systems, the reduction in particle size increases the surface area available for dissolution. In solid dispersions, the transformation of the crystalline drug into an amorphous state and the use of hydrophilic carriers improve the drug's wettability and dissolution behavior. SNEDDS and NLC formulations facilitate the rapid formation of colloidal emulsions upon contact with gastrointestinal fluids, resulting in the immediate solubilization of the drug.

In summary, diverse formulation strategies have shown significant potential in modulating the pharmacokinetic profile of ezetimibe, primarily by enhancing its dissolution, solubility, and absorption. Techniques such as solid dispersions, nanoparticle systems, and lipid-based carriers have consistently improved parameters, including AUC, Cmax, and Tmax, compared to conventional formulations or pure drug suspensions. These improvements are attributed to multiple formulation-driven mechanisms, including enhanced dissolution and subsequently improved absorption, facilitated by particle size reduction, amorphization, and the use of permeation-enhancing or lipid-based systems. However, while these findings provide a strong preclinical and mechanistic basis, their clinical relevance must be established through appropriately designed in vivo studies in humans. Factors such as variability in gastrointestinal physiology, metabolic pathways, and transporter interactions necessitate careful translation from bench to bedside.

Therapeutic Implications of Formulation Strategies

The previous section highlighted how various formulation strategies have successfully enhanced the pharmacokinetic properties of ezetimibe, as evidenced by improvements in AUC, Cmax, and Tmax. These findings suggest a substantial potential for overcoming the biopharmaceutical limitations of ezetimibe by utilizing suitable delivery systems. Building upon these pharmacokinetic benefits, it is essential to explore how such improvements translate into tangible therapeutic advantages. Although some studies have focused exclusively on pharmacokinetic or pharmacodynamic evaluations, several investigations have conducted both assessments in parallel. This dual in vivo approach provides a more comprehensive understanding of the relationship between enhanced systemic exposure and corresponding therapeutic efficacy. Table 2 presents the results of in vivo pharmacodynamic evaluations of different formulation strategies, covering both single-active formulations and combination systems.

Ezetimibe, as a single active pharmaceutical ingredient, has been shown to improve systemic pharmacodynamic profiles across various formulation strategies, including solid dispersions, co-crystals, inclusion complexes, nanoparticles, nanocrystals, NLCs, and micellar systems. Although some studies did not include prior pharmacokinetic evaluation, the positive outcomes observed in pharmacodynamic assessments still support the potential therapeutic benefits conferred by these advanced delivery systems. In general, these improvements are characterized by significant reductions in total

Table 2 Effect of Formulation Development on the Therapeutic Efficacy

Delivery System (Reference)	Formulation and Manufacturing Process	Pharmacodynamic Profiles
Ezetimibe in a solid dispersion system[37]	Solid dispersion using Polyvinylpyrrolidone K30 (PVP) as polymer via the solvent method (optimum in 1:5)	Solid dispersion more effectively reduced serum total cholesterol, LDL-C, and liver index in hyperlipidemic rats than the physical mixture ($p < 0.05$), with histological analysis confirming its superior effect on liver steatosis.
Ezetimibe in a co-crystal[29]	The imidazole co-crystal using a reaction crystallization method	Cocrystal demonstrated significantly greater improvements ($p < 0.05$) in lipid profile, liver enzyme levels, and atherogenic index compared to the pure drug.
Ezetimibe in a cyclodextrin inclusion complex[46]	Inclusion with β-cyclodextrin (CD) in a 1:1 molar ratio, along with solubilizing agents such as polyethylene glycol 1000 succinate (TPGS) and L-ascorbic acid-2-glucoside (AA2G)	Ezetimibe showed no significant antihypercholesterolemic effect versus control ($p > 0.05$), whereas all cyclodextrin-based complexes (EZE–CD, EZE–CD–AA2G, and EZE–CD–TPGS) produced marked cholesterol reductions ($p < 0.001$), with the HPβCD/TPGS ternary system outperforming both EZE–CD and EZE–CD–AA2G ($p < 0.05$)
Ezetimibe in chitosan nanoparticle[55]	Ionotropic gelation process using low molecular weight chitosan: TPP (1.75:2)	Nanoparticles showed a significant antihyperlipidemic effect, reducing serum TC, TG, LDL-C, VLDL-C, total lipids, and atherogenic index compared to hyperlipidemic and marketed product groups ($p < 0.05$)
Ezetimibe in nanocrystals[24]	Nanocrystalization by bottom-up precipitation methods using d-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS), and l-ascorbic acid-2-glucoside (AA2G) as stabilizer	The nanocrystal showed significantly greater reductions in TC and LDL levels than both pure ezetimibe ($p < 0.001$), as well as a superior TG-lowering effect ($p < 0.001$). While the HDL increase was similar across groups, confirming its enhanced antihyperlipidemic efficacy.
Ezetimibe in NLC[17]	Ultrasonication technique using oleic acid/ stearic acid as lipid phase and Tween 80 and Poloxamer 188 as surfactant	NLC system demonstrated a significant reduction in TC, TG, and LDL levels ($p < 0.05$), while notably increasing HDL levels compared to both the high-fat diet group and the ezetimibe suspension group
Ezetimibe in NLC[28]	NLC system using Capmul PG 8 as liquid oil, glycerol monostearate as solid lipid, and Poloxamer 188 as surfactant	NLC significantly reduced serum TC, TG, and LDL levels and increased HDL compared to HFD rats and pure EZE treatment ($p<0.001$), demonstrating superior efficacy over the pure drug.
Ezetimibe in NLC[73]	NLC by microemulsion technique using Solid lipid: Monosteol™; liquid lipid: Capryol™ 90 (ratio 1:1 w/w); Smix: Kolliphor® EL/ Transcutol® HP	The optimized EZE-loaded NLC significantly reduced total plasma cholesterol levels compared to both the high-fat diet control group ($p < 0.0001$) and the ezetimibe suspension group ($p < 0.05$).
Ezetimibe in miccelar system (MS)[76,77]	MS using Surfactant: Kolliphor® RH40 and hydrophylic carrier croscarmellose; Proportions of EZ: Kolliphor® RH 40 MS-I (1:0.25) and MS-II (1:0.75)	The micellar system (1:0.75) significantly outperformed the pure drug in improving the lipid profile of hyperlipidemic rats, showing a 0.74-, 0.60-, and 0.64-fold reduction in TC, TG, and LDL, respectively, and a 1.23-fold increase in HDL ($p < 0.05$), while pure drug only reduced TC and TG (0.82- and 0.70-fold) without significantly affecting LDL or HDL.

(*Continued*)

Table 2 (Continued).

Delivery System (Reference)	Formulation and Manufacturing Process	Pharmacodynamic Profiles
Ezetimibe and simvastatin in a co-amorphous system[93]	1:1 molar ratio of ezetimibe and simvastatin by the melt-quenched technique	The co-amorphous system exhibited a better lipid-lowering effect compared to the physical mixture, consistent with its enhanced bioavailability. Although ezetimibe plasma levels were undetectable, the formulation led to increased fecal cholesterol excretion and a reduction in NPC1L1 mRNA expression, indicating effective inhibition of intestinal cholesterol absorption.
Ezetimibe and atorvastatin in a solid dispersion system[100]	Solid dispersion using polymer PVP K30 at a comparison of 1:5 by the solvent method	The solid dispersion of ezetimibe and atorvastatin significantly reduced serum total cholesterol and LDL-C levels to 119.66 ± 8.76 mg/dL and 79.60 ± 9.97 mg/dL, respectively, which was better than the physical mixture group ($p < 0.05$). Additionally, it improved hepatic histology by minimizing steatosis and eliminating signs of inflammation.
Ezetimibe and atorvastatin in SNEDDS[27]	SNEDDS with Capryol 90 as oil phase, a combination of Tween 80®/Kolliphor RH40® as surfactant, and transcutol HP as cosurfactant	SNEDDS of atorvastatin/ezetimibe significantly reduced TC and non-HDL levels compared to the drug suspension ($p < 0.05$). After 12 hours of poloxamer induction, TC levels were elevated more than fourfold, but treatment with the optimized SNEDDS showed superior lipid-lowering efficacy.
Ezetimibe and atorvastatin in modified-release bilayer tablets[103]	Immediate atorvastatin and sustained-release ezetimibe layers using the wet granulation with HPMC K-100 as polymer	The bilayer tablets significantly reduced triglyceride levels (90.00 ± 25.12 mg/dL) compared to the negative control (155.66 ± 31.19 mg/dL, $p < 0.001$). Reductions were also observed in VLDL (20.00 ± 5.19 mg/dL) and total cholesterol (48.00 ± 2.64 mg/dL) levels, while HDL increased to 32.00 ± 3.61 mg/dL.
Ezetimibe micellar formulations with atorvastatin solid dispersions in a multiparticulate system[102]	Multiparticulate of ezetimibe micellar formulations with atorvastatin solid dispersions using Kolliphor RH40 and croscarmellose	The multiparticulate system significantly improved lipid profiles and liver function in diabetic rats. Even at low doses (2/6.7 mg/kg), it reduced TC by 25.37%, TG by 34.83%, and LDL by 44.13%, and lowered ALT and AST by 9.21% and 17.39%, respectively ($p < 0.05$), outperforming the physical mixture.
Ezetimibe and rosuvastatin in PLGA nanoparticles[106]	PLGA and Pluronic F-127 as polymers using nanoprecipitation	A nanoparticle-based formulation improved pharmacodynamic outcomes, markedly reducing serum levels of total cholesterol, triglycerides, LDL-C, and non-HDL-C, while increasing HDL-C. Compared to the suspension group, the nanoformulation achieved a greater lipid-lowering effect, with significant reductions in LDL-C ($p < 0.05$) and triglycerides ($p < 0.01$), alongside an increase in HDL-C ($p < 0.05$).

Abbreviations: AA2G, ascorbyl 2-glucoside; CD, cyclodextrin; EZE, ezetimibe; HDL, high-density lipoprotein; HPMC, hydroxypropyl methylcellulose; LDL, low-density lipoprotein; MS, micellar system; NLC, nanostructured lipid carriers; p, probability value (statistical significance); PLGA, poly(lactic-co-glycolic acid); SNEDDS, self-nanoemulsifying drug delivery system; TC, total cholesterol; TG, triglycerides; TPGS, D-alpha-tocopheryl polyethylene glycol 1000 succinate; VLDL, very-low-density lipoprotein.

cholesterol, triglycerides, and LDL levels. Furthermore, several studies also reported an increase in HDL levels, indicating a favorable modulation of the overall lipid profile. Several studies have demonstrated not only improvements in lipid profile but also superior effects on liver steatosis, hepatic enzyme levels, and the atherogenic index. In most cases, the anti-hyperlipidemia activity of these formulations was assessed in comparison with pure drug, drug suspensions, or physical mixtures. However, several studies have also included comparisons with marketed products, providing additional evidence of their therapeutic potential relative to existing therapies.

The chitosan-based ezetimibe nanoparticles exhibited markedly superior antihyperlipidemic efficacy compared to the marketed product. After four weeks of treatment in hyperlipidemic rats, the optimized nanoparticle formulation achieved significantly greater reductions in key lipid parameters: total cholesterol (51.5% vs 31.1%), triglycerides (53.2% vs 29.9%), LDL-C (74.0% vs 46.1%), VLDL-C (53.2% vs 29.9%), total lipids (51.1% vs 31.1%), and atherogenic index (65.7% vs 39.1%) compared to the marketed product ($p < 0.001$). While both formulations had a non-significant impact on HDL-C levels, the overall lipid-modulating performance of the nanoparticle system was considerably more potent, highlighting its promise not only as a more effective therapeutic approach but also as a potential alternative to existing commercial ezetimibe products in the management of dyslipidemia.[55]

Among the various formulation strategies, ezetimibe as a single active pharmaceutical ingredient has been extensively developed using NLC systems. One optimized NLC formulation was prepared using a microemulsion-based method incorporating Monosteol and Capryol 90 as lipid components, along with a surfactant mixture of Kolliphor EL and Transcutol HP. The system exhibited rapid self-dispersion and achieved nearly complete drug release within minutes under in vitro conditions. In vivo pharmacokinetic studies demonstrated that this NLC resulted in a fourfold increase in oral bioavailability compared to the ezetimibe suspension and a more than twofold increase compared to the marketed product. Moreover, the optimized NLC significantly reduced total plasma cholesterol levels in hyperlipidemic rats, showing a marked reduction versus both the high-fat diet control group ($p < 0.0001$) and the ezetimibe suspension group ($p < 0.05$), thereby demonstrating enhanced therapeutic efficacy.[73] Another study developed ezetimibe-loaded NLCs using ultrasonication, employing a lipid blend of oleic acid and stearic acid, with Tween 80 and poloxamer 188 as stabilizers. By adjusting the ratio of solid to liquid lipids, the formulation enabled modulation of the drug release profile. This NLC system demonstrated a significant lipid-lowering effect in hyperlipidemic rats, characterized by reductions in total cholesterol, triglycerides, and LDL-C levels ($p < 0.05$), along with a notable increase in HDL-C, when compared to both the high-fat diet control group and the ezetimibe suspension group.[17] Another formulation approach utilized NLCs composed of Capmul PG 8 as the liquid lipid, glycerol monostearate as the solid lipid, and Poloxamer 188 as the surfactant. This system demonstrated significant lipid-lowering activity, as evidenced by reductions in serum total cholesterol, triglycerides, and LDL-C levels, along with an increase in HDL-C, compared to both high-fat diet (HFD) rats and pure ezetimibe treatment ($p < 0.001$).[28]

Improvements in pharmacodynamic profiles were observed not only with ezetimibe as a single agent but also when used in combination forms. These enhancements were reflected in better lipid profiles in animal models treated with advanced formulation strategies, compared to those receiving drug suspension or physical mixtures. The combination of ezetimibe and atorvastatin has been more extensively developed compared to other combination systems. This may be attributed to their complementary mechanisms of action and the clinical relevance of dual lipid-lowering therapy. Various advanced delivery systems, including solid dispersions, SNEDDS, modified-release bilayer tablets, and multi-particulate systems, have been formulated for this combination, showing promising pharmacodynamic profiles with improved lipid-lowering effects.

Several studies focusing on the development of ezetimibe in combination formulations have conducted comprehensive investigations, clearly demonstrating the impact of formulation strategies on various parameters, including in vitro drug release, as well as pharmacokinetic and pharmacodynamic performance. As an example, a self-nanoemulsifying drug delivery system (SNEDDS) combining ezetimibe and atorvastatin was formulated using Capryol 90 as the oil phase, a surfactant blend of Tween 80 and Kolliphor RH40, and Transcutol HP as the co-surfactant. In vitro, the system achieved rapid and complete drug release (>99% for both drugs), significantly outperforming the pure drug suspensions (<8%). The SNEDDS demonstrated markedly improved pharmacokinetic performance, with relative oral bioavailability increasing by approximately 377% for ezetimibe and 355% for atorvastatin compared to their respective pure drug forms. In a hyperlipidemic rat model, this formulation significantly reduced total cholesterol and non-HDL levels ($p < 0.05$), confirming its superior lipid-lowering efficacy.[27] Another promising approach utilized PLGA nanoparticles to co-deliver ezetimibe and rosuvastatin, prepared via nanoprecipitation using PLGA and Pluronic F-127 as polymers. The formulation exhibited sustained drug release exceeding 90% over 24 hours. Pharmacokinetic evaluation revealed significant enhancements in oral bioavailability, with relative increases of approximately 247% for ezetimibe and 268% for rosuvastatin compared to their respective suspensions. Compared to the drug suspension, the nano-formulation

significantly reduced LDL-C ($p < 0.05$) and triglycerides ($p < 0.01$), while increasing HDL-C ($p < 0.05$), demonstrating superior pharmacodynamic effects.

The above discussion highlights that various delivery systems have demonstrated improvements in antihyperlipidemic effects in preclinical in vivo studies. These findings are encouraging and indicate the potential of such formulations to enhance therapeutic outcomes. However, translation to human use requires further comprehensive evaluations. In addition to confirming pharmacodynamic effects, studies should include pharmacokinetic assessments in humans, safety and toxicity profiling, as well as bioavailability or bioequivalence testing. These steps are crucial to ensure both efficacy and safety prior to clinical application.

Safety Considerations of Advanced Ezetimibe Formulations

Safety assessment represents a critical component in the development of advanced drug delivery systems, particularly for chronic therapies such as lipid-lowering agents. While innovative formulations offer substantial improvements in solubility, bioavailability, and therapeutic outcomes, their altered physicochemical properties and delivery platforms may introduce new biocompatibility or toxicity concerns. Moreover, enhanced systemic exposure may theoretically increase the risk of dose-related adverse effects.

Despite these considerations, several studies have demonstrated encouraging safety profiles for specific advanced ezetimibe formulations. For example, NLC of ezetimibe, evaluated via MTT cytotoxicity assays, showed significantly higher cell viability in normal Vero cells after 72 hours of exposure compared to the pure drug, indicating a lower cytotoxic potential.[28] Similarly, ezetimibe-loaded PLGA-based nanoparticles, such as lipid-coated ultra-small mesoporous silica systems (LUMNs), underwent acute oral toxicity testing at doses up to 5000 mg/kg. The results showed no mortality, behavioral abnormalities, or significant alterations in organ weights, hematological parameters, serum biochemistry, or histopathology, placing the formulation under GHS Category 5 ($LD_{50} > 2000$ mg/kg) and confirming good biocompatibility.[54]

The safety results from these studies provide an initial indication that advanced ezetimibe formulations may be generally well tolerated. However, toxicity remains an important consideration, as most ezetimibe-based systems have yet to undergo comprehensive toxicological evaluations beyond pharmacokinetic and efficacy assessments. Given that lipid-lowering therapies are typically administered over long durations, it is necessary to investigate further potential long-term risks related to altered drug disposition, such as drug accumulation, metabolite toxicity, or organ-specific effects that may not be apparent in short-term studies. Therefore, future safety assessments should progress beyond preclinical investigations and include well-designed clinical evaluations. Additionally, regulatory guidelines underscore the importance of ongoing safety monitoring throughout product development to ensure patient safety during extended use. In conclusion, further systematic studies are warranted to clarify long-term safety parameters, including potential toxicity, biocompatibility, and organ-specific effects.

Limitations and Future Directions

Despite substantial progress in the development of advanced ezetimibe formulations, several limitations remain that constrain their complete clinical translation. Many systems have shown promising in vitro performance, particularly in enhancing solubility and drug release. However, a significant number of studies are still limited to early-stage evaluations, and the correlation between in vitro behavior and in vivo outcomes is not always straightforward. Therefore, further investigations using appropriate pharmacokinetic and pharmacodynamic models are necessary to confirm their therapeutic relevance.

While some systems have been supported by comprehensive preclinical evaluations, including pharmacokinetic and pharmacodynamic data, safety profiling remains a critical aspect that is often overlooked. Given the diversity of excipients and delivery systems used, as well as the potential for increased systemic exposure, thorough safety assessments are essential to ensure tolerability and minimize toxicity risks. Moreover, the absence of stability studies under various storage conditions in some systems poses an additional barrier, as long-term stability is vital for formulation viability and successful commercialization. Addressing these gaps through systematic in vivo, safety, and stability assessments will be essential to advance these systems toward clinical application.

Moving forward, the clinical translation of ezetimibe-based innovations will require a strategic and stepwise approach, aligned with the characteristics of each formulation and its intended clinical role. For systems incorporating novel delivery technologies, excipients, or mechanisms that significantly alter pharmacokinetics, early-phase clinical trials remain essential to establish human safety, bioavailability, and dose-response relationships. These parameters cannot be fully predicted from preclinical models.

Ensuring long-term safety remains a key consideration. Although several advanced formulations have demonstrated low cytotoxicity and minimal acute toxicity in early evaluations, further toxicological studies are necessary. Moreover, successful clinical implementation will also depend on manufacturability and regulatory readiness. Formulations should be designed for scalable, cost-effective, and GMP-compliant production. Early engagement with regulatory authorities and adherence to established guidelines will be essential to facilitate the transition from laboratory development to clinical application.

In parallel, the therapeutic scope of ezetimibe is expanding through fixed-dose combinations with agents targeting common cardiometabolic comorbidities.[110] For example, the combination of ezetimibe, atorvastatin, and antihypertensive agents such as amlodipine has demonstrated favorable clinical outcomes in patients with both hypercholesterolemia and hypertension.[111] Other studies have explored triple combinations involving ezetimibe, rosuvastatin, and perindopril to simultaneously manage dyslipidemia and elevated blood pressure within a single formulation.[112]

Overall, the successful development and clinical implementation of advanced ezetimibe formulations will depend on comprehensive research, thorough safety evaluations, and careful integration of clinical and regulatory considerations. With these strategic efforts, innovative ezetimibe formulations have the potential to offer enhanced therapeutic benefits and improve the quality of life for patients with lipid disorders and cardiometabolic diseases.

Conclusions

The advancement of ezetimibe formulation strategies, including solid-state modifications, particle size reduction, and lipid- or surfactant-based approaches, has consistently demonstrated improved dissolution profiles, effectively addressing the drug's intrinsic solubility limitations. Optimization of excipients, manufacturing methods, and system composition remains critical for maximizing these improvements. Various delivery systems, such as solid dispersions, inclusion complexes, cocrystals, nanoparticles, SNEDDS, SLNs, and NLCs, have shown enhanced systemic exposure and superior lipid-lowering efficacy in preclinical models. In addition to single-agent therapy, advanced strategies have also been developed for the combination delivery of ezetimibe with various statins, including simvastatin, atorvastatin, rosuvastatin, and lovastatin, demonstrating added pharmacological synergy and formulation potential.

To fully realize the clinical benefits of these advanced formulations, further research is needed to establish long-term safety profiles and to conduct clinical trials. Such studies are essential not only to confirm therapeutic efficacy but also to assess potential improvements in patient adherence, quality of life, and cost-effectiveness. These factors will support the successful translation of innovative ezetimibe formulations into effective treatments for patients with dyslipidemia.

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Disclosure

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