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Review Article

Lipid-Based Nanocarriers For Enhancing The Bioavailability Of Telmisartan: A Comprehensive Review

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ABSTRACT

Telmisartan is an effective angiotensin II receptor blocker, but two problems keep limiting it. It barely dissolves in water, and the liver breaks down most of it before it gets a real chance to act. Together these create absorption that varies wildly, not only between patients but even within the same patient across doses, which is a real concern for a drug with such a narrow therapeutic window. This is a textbook BCS Class II problem, and it is what keeps holding this drug back clinically. Nanotechnology has spent the last couple decades chipping away at this exact issue. Lipid-based carriers such as solid lipid nanoparticles, nanostructured lipid carriers, liposomes, and self-emulsifying systems can raise solubility, ease membrane permeation, and even route drugs through the lymphatic system to bypass first-pass metabolism, while also protecting hydrophobic drugs from breaking down before reaching their target. This review centers on lipid-based nanocarriers designed for telmisartan delivery. Telmisartan's physicochemical properties, key formulation considerations, manufacturing methods, characterization approaches, and the correlation between in vitro and in vivo results are all examined, along with recent studies assessing where bioavailability and therapeutic outcomes have genuinely improved. Regulatory considerations, scale-up challenges, and future directions round out the discussion, connecting mechanistic understanding with practical formulation strategy to give a solid foundation for designing lipid-based delivery systems for poorly soluble drugs like telmisartan

1. INTRODUCTION

Hypertension remains one of the largest health burdens worldwide, driving a significant share of cardiovascular illness and death, particularly in developing countries where aging populations and shifting lifestyles are making things worse; pharmacological blood pressure control matters enormously, since the alternative is stroke, heart attack,

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or kidney failure.[1] Angiotensin II receptor blockers have gained a larger role in antihypertensive treatment recently, largely due to their safety profile and longer duration of action.[2] Telmisartan stands out among them, binding tightly to its receptor and remaining active in the body for an extended period, which explains its frequent clinical use, yet its poor water solubility and low oral bioavailability continue to undercut that potential.[3]

By the Biopharmaceutical Classification System, telmisartan lands in Class II: high permeability, but low solubility. For drugs like this, dissolution is the bottleneck that decides everything downstream, so plasma levels bounce around and therapeutic effects are not consistent, which is the whole reason smarter delivery strategies need to exist.[4] Its solubility also depends heavily on pH and tanks in acidic environments such as the stomach, leading to incomplete disintegration and weaker absorption, and first-pass metabolism then takes another bite out of it before it even reaches systemic circulation.[5] Various fixes have been tried over the years, including solid dispersions, cyclodextrin complexes, and nanosuspensions; these improve solubility somewhat but tend to run into trouble with stability, reproducibility, and scale-up, which is part of why lipid-based delivery systems have been gaining traction instead.[6]

Lipid-based nanocarriers are a promising way to push bioavailability higher for drugs that do not dissolve well on their own. They lean on the body's own physiological lipids to solubilize the drug and push it toward absorption through the intestinal lymphatic pathway, and because they can dodge hepatic first-pass metabolism, they can meaningfully boost how much drug makes it into systemic circulation.[7] It is not just about solubility either; these carriers also help drugs cross biological membranes more easily, since the lipids and surfactants improve how well the drug interacts with the intestinal lining, and some systems go a step further and block efflux transporters like P-glycoprotein, letting more drug build up inside cells instead of getting pumped back out.[8]

A handful of lipid nanocarrier types have been developed at this point, SLNs, NLCs, liposomes, and SEDDS, each bringing something different in drug loading capacity, stability, and release behavior, which is exactly why they work so well for hydrophobic drugs like telmisartan.[9] Recent work on lipid-based telmisartan formulations has shown real gains in pharmacokinetics and therapeutic effect, a solid sign that lipid nanocarriers could genuinely solve the problems that have dogged this drug, though formulation complexity, scale-up, and regulatory approval still stand in the way before these systems move from bench to clinic.[10]

The structure of these lipid nanocarriers shapes almost everything downstream: drug loading, release rate, formulation stability, and absorption efficiency. NLCs came about as a fix for SLNs' weaknesses, low drug loading and drug expulsion during storage, by blending solid and liquid lipids into a less ordered matrix that holds the drug better and stays more stable; SLNs, for context, were the original lipid carrier, built on a rigid lipid matrix.[11] Liposomes, made from phospholipid bilayers, bring excellent biocompatibility and fuse with membranes well, while SEDDS spontaneously form fine emulsions once they hit gastrointestinal fluids, increasing surface area and driving absorption; lipid-based carriers in general can also tweak membrane fluidity and block efflux transporters, boosting how much drug is absorbed inside enterocytes.[12]

More recently, formulation scientists have leaned on Quality by Design (QbD) approaches to systematically optimize these carriers, mainly to nail down reproducibility, scalability, and regulatory compliance.[13] Better analytical tools, such as molecular modeling, X-ray diffraction, and differential scanning calorimetry, have given researchers a much clearer picture of how these systems behave structurally and functionally, with recent studies confirming significant improvement in pharmacokinetic parameters such as Cmax and AUC.[8] Despite these encouraging results, successful commercialization is still hampered by large-scale production, long-term stability, and regulatory issues; even so, the versatility and multipurpose nature of lipid-based nanocarriers, along

with the growing focus on customized treatment, demonstrate their potential as cutting-edge delivery systems for overcoming telmisartan's biopharmaceutical constraints.

2. TELMISARTAN: PHARMACOLOGICAL PROFILE AND BIOPHARMACEUTICAL CHALLENGES

2.1 Chemical And Physicochemical Characteristics

Telmisartan belongs to the biphenyl tetrazole class of angiotensin II receptor blockers and is structurally distinct from losartan or valsartan, with two benzimidazole rings fused onto a biphenyl carboxylic acid group, making it highly lipophilic (Log P ~7.2), near the top of the list among ARBs for fat solubility.[5] It has a molecular weight of 514.62 g/mol and a pKa around 4.1, and dissolves poorly in water across most of the physiological pH range, though solubility ticks up slightly in more acidic conditions.[5] It is also highly crystalline, melting between 261°C and 263°C, and shows polymorphism, both of which work against dissolution and oral absorption.[14] Despite this, it is classified as BCS Class II rather than Class IV, since Caco-2 studies show it crosses membranes reasonably well; solubility is the real problem.[3]

2.2 Pharmacodynamics And Therapeutic Applications

Telmisartan lowers blood pressure by selectively and non-competitively blocking angiotensin II type 1 receptors within the renin-angiotensin-aldosterone system, suppressing vasodilation-blocking effects, cutting aldosterone secretion, and reducing sodium and water retention; it also dissociates from the AT1 receptor unusually slowly once bound, which largely explains its long-lasting effect.[15] Beyond RAAS blockade, telmisartan acts as a partial agonist at PPAR-γ, improving insulin sensitivity and glucose and lipid metabolism, and clinical studies have linked its use to a lower risk of developing diabetes over time.[16] Newer research also points to anti-inflammatory effects via NF-κB suppression and possible neuroprotective benefits from modulating brain AT1 receptors, opening interest in telmisartan for stroke, Alzheimer's disease, and cognitive decline.[17]

2.3 Pharmacokinetics And Bioavailability Challenges

Once swallowed, telmisartan is absorbed mostly in the proximal small intestine, with peak plasma concentration appearing between half an hour and ninety minutes after dosing. Oral bioavailability swings considerably, both between patients and within the same patient across doses: it averages around 42% at a 40 mg dose but climbs to roughly 58% at 160 mg, mostly because higher doses improve solubilization and partly saturate intestinal efflux mechanisms.[18] High-fat meals shift AUC in a dose-dependent way, since they ramp up bile secretion and pancreatic lipase activity, temporarily helping this lipophilic drug dissolve better in the gut lumen.[19] Telmisartan shows extremely high plasma protein binding (>99.5%), primarily to albumin and α1-acid glycoprotein, and a large apparent volume of distribution (~500 L), indicating extensive tissue distribution; it is eliminated predominantly through fecal excretion after glucuronidation to an inactive acyl-glucuronide metabolite, with minimal renal elimination.[20]

Although telmisartan has a long elimination half-life of nearly 20 to 24 hours supporting once-daily dosing, substantial variability in Cmax and AUC remains a major limitation, associated with pH-dependent solubility, crystal size differences, limited gastric residence time, and dissolution-rate-limited absorption.[21] Conventional formulations therefore often fail to provide optimal bioavailability unless combined with strategies such as particle size reduction, amorphization, complexation, or lipid-based delivery systems, which maintain drug solubilization during transit and stimulate lipid digestion processes, including bile salt secretion and mixed micelle formation, improving intestinal absorption.[22]

3. LIPID-BASED DRUG DELIVERY SYSTEMS: THEORETICAL FRAMEWORK

3.1 Classification And Overview Of LBDDS

Pouton's Lipid Formulation Classification System (LFCS) categorizes lipid-based formulations into four types based on composition, dispersion behavior, and anticipated in vivo performance.[23] Type I contains only triglycerides and mixed glycerides without surfactants, relying entirely on bile salt and pancreatic lipase secretion for gastrointestinal dispersion. Type II incorporates lipid-soluble surfactants (HLB < 12) alongside oils, forming coarse emulsions upon aqueous dilution. Type III systems self-emulsify into fine nano-dispersions, split into IIIA (moderate surfactant with water-miscible co-surfactants) and IIIB (heavier surfactant and co-solvent content, minimal oil), while Type IV skips oil entirely, relying only on surfactants and co-solvents to solubilize the drug through micelle formation.[24]

Given telmisartan's high lipophilicity (Log P ~7.2), Types I and II load the drug well since it has a strong affinity for triglyceride matrices, but the drug can precipitate once it hits the diluted intestinal environment. Types III and IV form smaller droplets and emulsify faster, but with less oil, may struggle to keep telmisartan dissolved throughout its transit.[25] Picking the right LFCS type comes down to weighing solubilization capacity, emulsification efficiency, and resistance to precipitation against formulation needs.[26]

3.2 Mechanisms Of Bioavailability Enhancement

Lipid-based nanocarriers boost telmisartan's bioavailability through several mechanisms that work together at different points along the gastrointestinal tract.[26]

3.3 Improving Dissolution And Maintaining Supersaturation

Because telmisartan arrives already dissolved in a lipid matrix, LBDDS sidesteps the dissolution bottleneck that normally limits absorption for BCS Class II drugs. Once the vehicle hits gastrointestinal fluid, it breaks into tiny droplets or nanoparticles, massively increasing surface area and keeping drug concentrations above the crystalline solubility limit right where absorption happens. Adding polymeric precipitation inhibitors such as HPMC, PVP, or HPMCAS (supersaturable SEDDS) helps stabilize this supersaturated state further, since these polymers slow nucleation and crystal growth through hydrogen bonding with telmisartan's functional groups.[27]

3.4 Lymphatic Drug Transport

For highly lipophilic drugs like telmisartan (Log P over 5), absorption through the intestinal lymphatic system via chylomicrons is important because it completely bypasses hepatic first-pass metabolism. After lipid digestion, the resulting monoglycerides and fatty acids are reassembled into triglycerides inside enterocytes, combining with the drug to form chylomicrons that head into the lymphatic system rather than straight into the bloodstream. Studies in rats with cannulated mesenteric lymph ducts have shown noticeably higher telmisartan levels after lipid formulations compared to plain aqueous suspensions.[28]

3.5 Inhibition Of P-Glycoprotein Efflux And Permeation Enhancement

Telmisartan is a substrate for P-glycoprotein, which normally pumps it back out of intestinal cells. Several lipid excipients commonly used in LBDDS, such as Cremophor EL, Labrasol, Tween 80, and Poloxamer 188, interfere with P-gp by fluidizing cell membranes and inhibiting its ATPase activity, cutting down efflux and boosting net absorption on top of the formulation's solubilization benefit.[29] Medium-chain fatty acids and their monoglycerides can also temporarily loosen tight junctions between intestinal cells by acting on proteins like claudins and occludins, opening up paracellular transport, while nanoparticulate lipid carriers can be taken up through M cells at Peyer's patches via endocytosis and transcytosis, giving the drug another route in besides ordinary transcellular diffusion.[30] On top of this, lipids trigger cholecystokinin secretion, which slows gastric emptying and stretches out the window of time available for absorption in the proximal small intestine; solid lipid carriers such as SLNs and NLCs add a further layer by releasing the drug slowly through diffusion-controlled mechanisms, smoothing out Cmax variability, a real advantage for a once-daily antihypertensive like telmisartan.[31]

4. SOLID LIPID NANOPARTICLES (SLNS) FOR TELMISARTAN DELIVERY

4.1 Conceptual Foundation, Structural Architecture, And Preparation

Solid lipid nanoparticles, first introduced by Müller and Lucks in the early 1990s, are colloidal carriers of 50 to 1000 nm composed of biocompatible solid lipids that remain crystalline at physiological temperature, stabilized by a surfactant shell. Drug molecules are entrapped, adsorbed, or dissolved within the rigid lipid core in one of three configurations: homogeneous matrix, drug-enriched shell, or drug-enriched core; for telmisartan, given its high lipophilicity (Log P ~7.2), the homogeneous matrix model predominates under rapid cooling, while slower crystallization favors shell enrichment.[32] Common solid lipids include glyceryl monostearate, Compritol 888 ATO, Precirol ATO 5, cetyl palmitate, stearic acid, and carnauba wax, selected for their biocompatibility, regulatory acceptance, and capacity to form stable matrices, with surfactant stabilizers such as Poloxamer 188, Tween 80, lecithin, and Cremophor RH40 used alone or in combination for electrosteric stabilization against aggregation during storage.[33] The gold-standard, GMP-compatible, solvent-free Hot High-Pressure Homogenization (Hot HPH) method dissolves telmisartan in molten lipid, emulsifies it in a hot aqueous surfactant solution, and homogenizes it at 500 to 1500 bar over several cycles.[34] Cold HPH, built for heat-sensitive drugs, freezes the drug-lipid melt rapidly in liquid nitrogen, grinds it into microparticles, then homogenizes it under high pressure in cold surfactant solution, typically producing 150 to 400 nm particles with PDI under 0.3, zeta potential of −20 to −40 mV, and entrapment efficiency of 68 to 95%, though particles tend to be larger and less uniform than with hot HPH.[35] The microemulsion template method rapidly disperses a hot drug-lipid microemulsion into cold water (2°C to 4°C) before Ostwald ripening sets in, forcing quick recrystallization into 50 to 200 nm particles without high-energy equipment, though reproducibility hinges on tightly controlling microemulsion composition.[36]

4.2 Characterization, In Vivo Performance, And Stability

DLS is standard for measuring size and PDI, with zeta potential beyond ±30 mV suggesting good colloidal stability and particles under 200 nm favoring lymphatic uptake with less clearance by Peyer's patch macrophages.[37] DSC shows a suppressed lipid melting peak and loss of telmisartan's usual 261°C peak, indicating amorphous or molecularly dispersed drug within the matrix, and XRD confirms this with weaker crystalline peaks, both pointing to higher apparent solubility.[38] Well-optimized SLNs typically reach entrapment efficiency above 80%, with drug loading between 3% and 12% by weight depending on lipid composition and drug-to-lipid ratio.[39] In vitro release testing in FaSSIF and FeSSIF media shows biphasic release, two to four times faster than plain drug suspension at physiological pH, with an initial burst followed by sustained diffusion.[40]

Compritol 888 ATO-based telmisartan SLNs showed a 2.76-fold increase in oral bioavailability versus plain suspension in Wistar rats, attributable to the drug staying amorphous, enhanced lymphatic transport, P-gp efflux inhibition, longer gut residence via mucoadhesion, and the lipid matrix's own permeation-enhancing effect.[41] A known limitation is the shift from metastable alpha or beta-prime lipid forms to the stable beta form during storage, which tightens the lipid structure and leads to drug expulsion, particle growth, and slower release; common fixes include blending lipids, adding liquid lipid to disrupt crystallinity, and optimizing surfactant levels to hold stability through shelf life.[42]

5. NANOSTRUCTURED LIPID CARRIERS (NLCS) FOR TELMISARTAN DELIVERY

5.1 Conceptual Evolution And Formulation Design

The second generation of solid lipid nanocarriers, NLCs, were first presented by Müller, Radtke, and Wissing in 2002, created specifically to overcome SLN limitations by introducing liquid lipid into the solid matrix. The resulting structurally disordered core gives increased drug loading, decreased polymorphic

transitions, minimal drug expulsion, and modulated release kinetics, and can follow one of three structural models: multiple type (oil nanocompartments scattered within the solid matrix), amorphous type (a fully amorphous matrix eliminating crystalline drug expulsion), or imperfect type (spatial lattice defects from small oil addition).[43]

The most important formulation variable is the solid-to-liquid lipid ratio; ratios between 70:30 and 90:10 w/w provide the best drug loading, stability, and controlled release. Common solid lipids include Compritol 888 ATO, Precirol ATO 5, GMS, and cetyl palmitate, while liquid lipid components include oleic acid, Labrafil M1944CS, Miglyol 812, and Capmul MCM, with surfactant systems such as Poloxamer 188/lecithin, Tween 80/Span 80, and Cremophor RH40/PEG 400 stabilizing dispersion. QbD approaches using Box-Behnken, central composite, and D-optimal designs have consistently produced optimized NLCs with particle size 100 to 250 nm, PDI < 0.25, zeta potential > −30 mV, and EE% > 85%.[44]

5.2 Comparative Performance, Surface Modification, Stability, And Scale-Up

In a systematic comparison of telmisartan SLNs and NLCs (Compritol/oleic acid, 80:20), Bhaskar et al. (2022) found NLCs superior in EE% (91.3% vs. 78.6%), particle size (178 nm vs. 242 nm), and 6-month physical stability at 25°C/60% RH, attributed to the structurally imperfect matrix's increased drug accommodation and liquid lipid-mediated suppression of polymorphic transitions. In vivo pharmacokinetic studies in Wistar rats confirmed a 3.8-fold increase in oral bioavailability for NLCs versus a 2.7-fold improvement for SLNs, along with more stable plasma profiles and fewer peak-to-trough fluctuations.[45]

Chitosan-coated NLCs take advantage of the polymer's mucoadhesive and permeation-enhancing properties, with the positively charged shell (+22 mV, shifted from −28 mV) electrostatically interacting with intestinal mucus to prolong residence time and open tight junctions, resulting in a 4.6-fold increase in AUC0-∞ compared to uncoated drug suspension.[46] Well-formulated telmisartan NLCs maintained particle size change < 10%, PDI < 0.3, EE% reduction < 5%, and drug content > 95% under ICH Q1A accelerated conditions (40°C/75% RH, 6 months); lyophilization with 5% w/v trehalose gave the best cryoprotection, and pilot-scale production using microfluidizer and membrane emulsification technologies confirmed batch-to-batch reproducibility (RSD < 5%) and aseptic processing compatibility.[47]

6. SELF-EMULSIFYING AND SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEMS (SEDDS/SNEDDS)

6.1 Principles, Component Selection, And Phase Behavior

SEDDS and SNEDDS are isotropic mixtures of oils, surfactants, and co-solvents in which telmisartan is dissolved at high concentration, spontaneously forming oil-in-water emulsions upon gastrointestinal dilution driven solely by intestinal peristalsis. SEDDS produces coarse emulsions of 100 to 300 nm, while SNEDDS generates nano-droplets below 100 nm, yielding transparent nanoemulsions with greater interfacial surface area, improved gravitational stability, and more reproducible in vivo absorption.[25]

The oil phase produces fatty acids and monoglycerides that aid lymphatic uptake while acting as a pancreatic lipase substrate and telmisartan solvent; with telmisartan solubility of 15 to 45 mg/mL versus under 0.1 µg/mL in water, screening favors Labrafil M1944CS, Capmul MCM, oleic acid, and castor oil. High-HLB (>12) non-ionic surfactants such as Tween 80, Cremophor RH40, Cremophor EL, Labrasol, and Solutol HS15 are favored for their emulsification efficiency, proven safety, and reduced gastrointestinal irritation, while co-surfactants such as Transcutol P, PEG 400, and Span 80 enhance drug loading, prevent post-dilution precipitation, and enable sub-100 nm droplets; Transcutol P is particularly effective for telmisartan, offering solubility of ~50 mg/mL alongside strong emulsification contribution.[48]

Pseudoternary phase diagrams, mapping oil, Smix (surfactant-co-surfactant blend), and water, identify the compositional zone where clear, stable nanoemulsions

spontaneously form, with higher Smix ratios (1:1 to 4:1) typically increasing this zone and decreasing droplet size; DoE approaches such as D-optimal mixture, simplex lattice, and central composite designs have found ideal ratios producing telmisartan SNEDDS with droplet sizes of 28 to 65 nm, PDI 0.12 to 0.22, and EE% > 95%, confirmed thermodynamically stable through heating-cooling cycling, centrifugation stress, and freeze-thaw cycling without phase separation or drug precipitation.[49]

6.2 In Vitro And In Vivo Performance, And Solid SNEDDS

In vitro dissolution in biorelevant FaSSIF media showed >85% telmisartan release from SNEDDS within 30 minutes compared to <35% from the commercial tablet, more than a two-fold improvement in dissolution efficiency. An optimized Capmul MCM/Cremophor RH40/Transcutol P (20:60:20) SNEDDS showed a 4.2-fold AUC0-∞ enhancement, a 2.3-fold Cmax increase, and a decreased Tmax (0.75 h vs. 1.5 h) compared to the reference tablet in Wistar rats.[50]

To address issues with liquid formulations, such as drug migration and patient preference for solid dose forms, liquid SNEDDS can be adsorbed onto solid carriers like Aerosil 200, Neusilin US2, or Sylysia 320 and converted into tablets or capsules. Telmisartan S-SNEDDS on Neusilin US2 maintained self-emulsification performance and in vivo pharmacokinetics equivalent to the parent liquid SNEDDS while providing significantly better flowability, compressibility, and long-term physical stability suited to conventional manufacturing.[51]

7. NANOEMULSIONS AND MICROEMULSIONS FOR TELMISARTAN

7.1 Characteristics And Preparation Methods

Nanoemulsions are oil droplets of roughly 20 to 200 nm dispersed in water, held stable by surfactant and co-surfactant molecules at the interface. They are thermodynamically metastable but kinetically stable, needing mechanical energy to form yet remaining stable for months or years if stored properly, and their tiny droplet size gives better mucosal penetration, more surface area for absorption, stronger resistance to creaming, and better optical clarity; for telmisartan this sidesteps the dissolution bottleneck entirely since the drug is already dissolved in the oil phase.[52]

High-energy preparation methods include high-pressure homogenization, forcing a coarse telmisartan-oil emulsion through a valve at 500 to 1500 bar across multiple passes until droplets shrink to nanoscale, and ultrasonication, using acoustic cavitation at 20 kHz for 5 to 20 minutes to reach droplets of 60 to 150 nm. Low-energy methods work differently: phase inversion temperature heats the formulation past the surfactant system's inversion point then cools it quickly to trigger spontaneous nanodroplet formation, while spontaneous emulsification dissolves oil and surfactant in a water-miscible solvent so gradual water addition drives nanodroplet formation through solvent diffusion; done well, both low-energy routes can match the droplet sizes achieved with high-energy methods.[53]

7.2 Microemulsions And In Vivo Performance

Microemulsions differ from nanoemulsions in being thermodynamically stable, forming spontaneously once water, oil, surfactant, and co-surfactant combine in the right ratios as interfacial tension drops to near zero. Telmisartan oil-in-water microemulsions using oleic acid or Labrafil M1944CS as the oil phase, Cremophor EL as surfactant, and PEG 400 or Transcutol P as co-surfactant produce droplets of 15 to 80 nm with strong physical stability over 12 months of storage.[54] Both nanoemulsions and microemulsions dissolve much faster than commercial tablets, releasing the full drug dose within 20 to 45 minutes under biorelevant conditions, and oral bioavailability jumps 2.8- to 4.5-fold compared to crystalline drug solutions; unlike SLNs and NLCs, these systems avoid solid lipid crystallization altogether, so there is no drug expulsion issue, meaning more consistent release across shelf life.[55]

8. LIPOSOMES AND VESICULAR LIPID CARRIERS

8.1 Structure, Encapsulation, And Preparation

Liposomes are spherical vesicles with a watery core wrapped in one or more phospholipid bilayer membranes, letting them carry lipophilic drugs in the bilayer and hydrophilic drugs in the core at once. How well telmisartan is encapsulated depends on lipid composition, charge, and preparation method, since the drug (Log P ~7.2) tends to intercalate directly into the phospholipid bilayer; standard telmisartan liposomes typically use phosphatidylcholine as the main lipid alongside cholesterol at 30% to 40% mol, which closes gaps between bilayers, cuts membrane permeability, and extends drug retention.[56] The classic preparation approach is thin-film hydration (the Bangham method), producing MLVs downsized into SUVs through probe sonication or extrusion through 100 to 400 nm polycarbonate membranes; comparison studies have found that ethanol injection actually produces smaller, more uniform vesicles than thin-film hydration.[11]

8.2 Proliposomes, Phytosomes, And Niosomes

Proliposomes are dry, free-flowing powders that spontaneously turn into liposomal dispersions once hydrated; telmisartan proliposomes made via the slurry method, using sorbitol or mannitol as carriers, give stable dispersions of 150 to 300 nm with entrapment efficiency of 72% to 88%, offering better storage stability than liquid liposomes and easier incorporation into solid dosage forms.[57] Phytosomes lack an internal water compartment; instead the drug forms a direct stoichiometric complex with soy phosphatidylcholine through hydrogen bonding, showing a 2.4-fold increase in AUC over plain drug.[58] Niosomes use non-ionic surfactants such as Span 60, Span 80, Brij 35, or Tween 60 with cholesterol instead of phospholipids, and are cheaper and simpler to manufacture than conventional liposomes.[59] Telmisartan niosomes made using Span 60/Tween 60/cholesterol systems achieved particle sizes of 200 to 450 nm, zeta potentials of −25 to −35 mV, and EE% of 78% to 92%, with biphasic release and a 2.9-fold AUC0-∞ improvement over plain drug solution in Wistar rats, along with much lower interindividual variability.[59]

8.3 Transfersomes And Ethosomes For Transdermal Delivery

Going the transdermal route skips hepatic first-pass metabolism and gut absorption variability entirely. Transfersomes are ultra-deformable vesicles built with edge activators like sodium deoxycholate or Tween 80 that squeeze through skin pores via the transepidermal hydration gradient, achieving three- to five-fold better skin permeation in rat abdominal skin studies compared to a standard hydroalcoholic gel, with pharmacodynamic testing showing blood pressure lowering roughly comparable to an oral tablet. Ethosomes use phospholipid vesicles loaded with 20% to 45% ethanol by volume, where the ethanol both dissolves the drug and enhances permeation by extracting and loosening stratum corneum lipids.[21]

9. LIPID-POLYMER HYBRID NANOPARTICLES AND CUBOSOMES

9.1 Lipid-Polymer Hybrid Nanoparticles (LPHNPs)

LPHNPs combine lipid carriers with polymeric nanoparticles to get the best of both worlds: pure lipid systems solubilize drugs well and are biocompatible but mechanically unstable and prone to lipase breakdown, while polymer nanoparticles are sturdier and give controlled release but often cannot load enough lipophilic drug and can be somewhat toxic. LPHNPs address this with three layers: an outer DSPE-PEG2000 shell for stability and longer gut residence, a middle phospholipid layer (lecithin or DPPC) aiding membrane permeation, and an inner PLGA, PCL, or PLA polymer core holding the drug through hydrophobic interactions.[60] They are made either by single-step nanoprecipitation, self-assembling into particles of 120 to 220 nm with PDI under 0.20 and entrapment efficiency of 80% to 93%,[61] or by a two-step method where the polymer core is made first and coated separately with a lipid shell for more precise control.[62]

PLGA-lecithin-PEG telmisartan LPHNPs delivered a 5.1-fold jump in oral bioavailability, beating plain PLGA nanoparticles (3.2-fold) and lecithin-based SLNs (2.8-fold) under identical conditions.[63]

Cytotoxicity testing in Caco-2 and HEK293 cells showed over 90% viability at concentrations up to 500 µg/mL, notably better than uncoated PLGA particles, confirming that the lipid shell acts as a biocompatible buffer between polymer and cell membranes.[64]

9.2 Cubosomes

Cubosomes form when glyceryl monooleate or phytantriol self-assembles with water and a stabilizer such as Poloxamer 407, creating a nanostructured particle with a bicontinuous cubic internal architecture, essentially two separate water-channel networks divided by a curved lipid bilayer. Telmisartan loads exceptionally well into this structure since its polar carboxylic acid group and lipophilic rings let it sit in both the bilayer and the aqueous channels at once.[65] They are made through top-down fragmentation: molten GMO combined with aqueous telmisartan forms a bulk cubic gel, broken down into nanoparticles via HPH or ultrasonication with Poloxamer 407 stabilizing the result, giving particles of 150 to 300 nm with strongly negative zeta potential (−25 to −40 mV) and SAXS-confirmed cubic internal structure.[66] Drug release occurs through diffusion along these channels plus gradual breakdown of the monoglyceride matrix by intestinal lipases.[65] In vivo testing showed a 3.4-fold bioavailability boost over plain drug suspension and a 1.8-fold longer mean residence time compared to lipid nanoemulsions, hinting at more stable 24-hour blood pressure control.

10. COMPARATIVE ANALYSIS OF LIPID NANOCARRIER SYSTEMS

10.1 Particle Size, Colloidal Properties, And Drug Loading

SNEDDS and nanoemulsions consistently give the smallest telmisartan droplets of any lipid system (20 to 100 nm), thanks to high surfactant loads and energetic emulsification. SLNs and NLCs typically land bigger (150 to 400 nm), cubosomes and LPHNPs sit in between (120 to 300 nm), and liposomes and niosomes generate the largest vesicles (200 to 500 nm) without extrusion, reduced to 80 to 150 nm with 100 nm membrane extrusion. Zeta potential values are continuously negative (−20 to −45 mV) in most systems, reflecting ionization of phospholipid headgroups and surface fatty acids at physiological pH; chitosan-coated systems (+15 to +30 mV) are the exception, offering added mucoadhesive advantage through electrostatic interaction with mucin glycoproteins.[52]

Drug loading capacity and EE% directly determine the amount of carrier material needed per therapeutic dose, affecting formulation practicality and patient acceptance. Required carrier levels for the usual 40 mg telmisartan dose vary from about 400 mg for high-EE NLCs (~10% drug loading) to over 1000 mg for liposomes or niosomes, and greater loads pose real problems for capsule fill weight and palatability. LPHNPs and NLCs have the highest drug loading efficiency among solid carriers, typically EE% of 85% to 93%, while SNEDDS should theoretically give 100% drug loading since telmisartan is fully dissolved in the carrier, though post-dilution precipitation may lower the effective dissolved fraction available for absorption.[48]

11. COMPARATIVE ANALYSIS: FAST-DISINTEGRATING TABLETS VERSUS MOUTH-DISSOLVING FILMS OF TELMISARTAN

Both approaches target telmisartan's poor aqueous solubility, BCS Class II classification, and limited oral bioavailability, but through different dosage-form strategies. Gosavi et al. developed fast-disintegrating tablets (FDTs) using direct compression with superdisintegrants, achieving a disintegration time of 34 ± 0.19 seconds through Crospovidone's swelling and wicking action, versus 10 to 15 minutes for conventional tablets. Husain et al. developed a hydrocolloid-based mouth-dissolving film (MDF) incorporating telmisartan as a beta-cyclodextrin solid dispersion with HPMC E15 as film-forming polymer, disintegrating even faster (29 seconds) owing to its thin-film architecture (0.45 mm) and requiring no water at all, unlike FDTs which still generate a particle suspension.[67,68]

The two strategies also differ in how they address solubility. FDTs accelerate physical disintegration without altering telmisartan's crystalline state, so the drug still dissolves from its crystalline form after disintegration, releasing about 55.6% at 5 minutes and 99.4% at 30 minutes. The MDF's solid-dispersion pre-processing instead converts telmisartan to an amorphous, molecularly dispersed form before film formation, confirmed by a DSC shift of the melting endotherm, giving 91.83% cumulative release and over 60% release within 3 minutes in simulated salivary fluid; its buccal and sublingual absorption also lets a pre-gastric drug fraction bypass gastric pH limitations and first-pass metabolism entirely, a pathway unavailable to tablets or FDTs.[67,68]

Both forms substantially improve compliance over conventional tablets, particularly for geriatric, pediatric, and dysphagic patients, though the MDF offers the more complete solution, dissolving fully without any water requirement or gritty residue (Table 1). Overall, the mouth-dissolving film emerges as the more pharmacokinetically advantageous dosage form, owing to faster disintegration, amorphization-based solubility enhancement, longer demonstrated stability, and a unique pre-gastric absorption pathway, making it the more patient-centric option, particularly for geriatric hypertensive patients needing rapid onset of action.[67,68]

Table 1: Summary Comparison of Conventional Tablet, FDT, and MDF Formulations of Telmisartan

Parameter	Conventional Tablet	FDT (Gosavi et al., 2025)	MDF (Husain et al., 2022)
Disintegration Time	10–15 minutes	34 ± 0.19 seconds	29 seconds
Drug Release at 5 min	~10–15%	55.6%	>60% (salivary)
Drug Release at 30 min	~35–40%	99.4%	91.83%
Solubility Strategy	None	Particle size reduction	Solid dispersion (amorphization)
Water Requirement	Essential	Partial	None
Pre-gastric Absorption	No	No	Yes (buccal/sublingual)
First-pass Bypass	No	No	Partial (transmucosal fraction)
Drug Content	Variable	99.02%	93.77%
Stability Duration	Standard	2 months	6 months
Patient Compliance	Poor for dysphagic	Good	Excellent
Manufacturing Complexity	Simple	Simple	Moderate
Scalability	High	High	Moderate

12. STABILITY, MANUFACTURING SCALABILITY, AND QUALITY BY DESIGN (QBD) IN TELMISARTAN LIPID NANOCARRIER DEVELOPMENT

12.1 Comparative Stability And Scalability

Among telmisartan lipid nanocarrier systems, SNEDDS and S-SNEDDS show the best storage stability, with minimal change in drug content and self-emulsification capability over 24 months at room temperature. SLNs have the most troublesome stability profile owing to polymorphic transitions and drug expulsion, while NLCs show intermediate stability. Liposomes and niosomes retain reasonable stability (6 to 12 months refrigerated) when lyophilized or converted into proliposomes, and LPHNPs, owing to the stiffness of the polymer core, are more stable than pure lipid carriers, showing >95% drug content retention and <15% particle size change over 12 months at 25°C/60% RH.[69] SEDDS/SNEDDS are also the simplest and most scalable systems to manufacture, needing only basic liquid-component mixing, and Hot HPH-prepared SLNs and NLCs are similarly scalable to multi-hundred-kilogram batches; liposomes, cubosomes, and LPHNPs are more complex, requiring specialized equipment, inert-atmosphere and low-temperature processing, and thorough quality control, all raising production costs and timelines.[70]

12.2 QbD Framework, Critical Quality Attributes, And IVIVC

As defined in ICH Q8(R2), Q9, and Q10 guidelines, QbD is a systematic, science-based development approach emphasizing product and process understanding through quality risk management. Its application to telmisartan lipid nanocarrier development follows sequential steps: QTPP definition, CQA identification, risk assessment via Ishikawa diagrams and FMEA to prioritize CMAs and CPPs, DoE studies establishing quantitative CMA/CPP-CQA relationships, Design Space definition, and control strategy development.[71] Universally recognized CQAs include particle size (<300 nm), PDI (<0.3), zeta potential (>|20| mV), EE% (>80%), in vitro drug release at 2 and 24 hours, drug content uniformity (98 to 102% label claim), and physical stability under accelerated conditions; risk assessments typically flag solid lipid type and concentration, liquid lipid proportion, surfactant type and concentration, drug-to-lipid ratio, homogenization pressure, and cooling rate as the most important variables, with the resulting Design Space established for telmisartan NLC and SNEDDS formulations across multiple QbD studies.[69]

Using biorelevant FaSSIF (pH 6.5) dissolution medium and two-stage testing that replicates successive gastric and intestinal environments, Level A IVIVCs, the highest regulatory-value correlation type, have been developed for telmisartan NLC and SNEDDS formulations in rat models. PBPK models incorporating lipid digestion kinetics, intestinal solubilization capacity, lymphatic transport parameters, and enterocyte permeability now predict human pharmacokinetic outcomes from preclinical data with significantly better accuracy than traditional compartmental models, and a validated IVIVC could reduce the number of clinical pharmacokinetic studies needed for formulation optimization and bioequivalence demonstration by allowing in vitro dissolution data to serve as a regulatory surrogate.[72]

13. EMERGING AND NOVEL STRATEGIES IN LIPID NANOCARRIER DEVELOPMENT

13.1 Supersaturable SNEDDS And Stimulus-Responsive Carriers

Conventional SNEDDS face a catch-22: high surfactant levels are needed to form a good nanoemulsion, but those same levels speed up telmisartan precipitation once diluted in the gut. Supersaturable SNEDDS get around this by adding precipitation-inhibiting polymers such as HPMC, HPMCAS, PVP K30, or Eudragit L100-55 at low concentrations, which hinder crystal nuclei formation through steric effects and hydrogen bonding with telmisartan's functional groups. HPMCAS works particularly well, being amphiphilic enough to interact with both drug and aqueous fluid, with pH-sensitive solubility that activates specifically in the intestine; in

rat studies, adding just 0.1% to 0.5% HPMCAS stretched supersaturation from about 15 minutes to over 120 minutes, translating into an extra 1.5- to 2-fold bump in oral bioavailability compared to regular SNEDDS.[73]

Stimulus-responsive carriers add further precision: pH-responsive NLCs using ionizable lipids like DODAP release telmisartan faster at pH 5.5 to 6.0 than at physiological pH 7.4, useful for ischemic or inflamed cardiovascular tissue where local pH drops.[74]

13.2 Co-Delivery, Route-Specific Delivery, And Continuous Manufacturing

Combining telmisartan with amlodipine in SNEDDS or NLC co-formulations boosted bioavailability of both drugs, 3.8-fold for telmisartan and 2.9-fold for amlodipine, versus physically mixing the two, with synergistic blood pressure lowering in spontaneously hypertensive rats even at lower doses.[75] Co-loaded NLCs for telmisartan-rosuvastatin combination therapy similarly showed better oral bioavailability for both drugs and superior reductions in blood pressure, LDL cholesterol, and inflammatory markers in hyperlipidemic hypertensive rat models versus individual conventional formulations.[76]

Given telmisartan's neuroprotective qualities via brain AT1 receptor blockade, intranasal telmisartan NLCs with mucoadhesive polymers exploit the nose-to-brain pathway to bypass the blood-brain barrier, producing brain drug concentrations 4- to 6-fold higher than comparable oral doses and improving cognitive outcomes in a dementia model.[77] 3D-printed telmisartan SNEDDS filaments (hot-melt extruded with PVA or Kollicoat IR) have produced printed tablets with performance comparable to conventional S-SNEDDS tablets while offering on-demand dose adjustment.[78]

14. TOXICOLOGICAL AND SAFETY CONSIDERATIONS OF LIPID EXCIPIENTS

Most lipid excipients used in telmisartan nanocarriers, such as glyceryl monostearate, glyceryl behenate, Precirol ATO 5, lecithin, oleic acid, Miglyol 812, and Compritol 888 ATO, are GRAS-listed or already appear in the FDA's Inactive Ingredients Database for approved oral drugs. Phospholipids like soy phosphatidylcholine and egg lecithin are naturally occurring membrane components the body breaks down into fatty acids and glycerophosphocholine, making them well tolerated even with repeated dosing, and the PLGA and PCL polymers used in LPHNPs similarly break down through well-understood enzymatic hydrolysis into lactic acid, glycolic acid, and hydroxycaproic acid, with a solid safety track record in injectable products.[79]

15. REGULATORY FRAMEWORK AND SCALE-UP CHALLENGES

15.1 Approval Pathways And CMC Requirements

The FDA evaluates lipid nanocarrier formulations containing telmisartan using either the 505(b)(1) or 505(b)(2) NDA pathways, with the latter more frequently used for new formulations of approved drugs, relying on existing safety and efficacy data while requiring pharmacokinetic and pharmacodynamic evidence specific to the new formulation.[80] CMC submissions must thoroughly cover product composition, manufacturing process, process controls, analytical techniques, specifications, container-closure systems, and stability programs, with particular challenges around characterizing the multi-component lipid matrix, demonstrating particle size control throughout manufacturing, validating analytical techniques that differentiate encapsulated from free drug, and showing stability under pertinent storage and shipping stress.[81] ICH Q1A(R2) requires stability data under long-term (25°C/60% RH), intermediate (30°C/65% RH), and accelerated (40°C/75% RH) conditions for a minimum of 12 months before NDA filing, with testing extended to particle size, PDI, zeta potential, peroxide value, and anisidine value, since standard assays alone will not catch lipid oxidation or colloidal breakdown.

15.2 Bioequivalence Considerations

Unless there is a solid IVIVC-based case for a biowaiver, any telmisartan lipid nanocarrier

formulation aiming to compete with existing tablets must go through proper clinical pharmacokinetic bioequivalence testing in healthy volunteers.[15] Because telmisartan has such a pronounced food effect, the standard bioequivalence bar, a 90% confidence interval for AUC and Cmax ratios within 80% to 125% of the reference product, must be cleared in both fasted and fed states. The standard 40 to 80 mg reference-tablet dose will not work here, since preclinical data consistently shows these nanocarrier formulations pushing bioavailability up 4- to 5-fold and using the original dose would push exposure into dangerous territory; the dose needs adjusting downward before bioequivalence trials can begin, and pinning down the right dose calls for careful bridging studies to match systemic exposure against the reference product, adding real time and complexity to the regulatory path.[82]

16. FUTURE PERSPECTIVES

AI and machine learning are starting to reshape how telmisartan lipid nanocarriers are developed, pointing toward promising formulations without endless rounds of trial and error, while deep learning automatically analyzes nanoparticle shape and size from microscopy images, speeding up characterization. Generative AI could help design new lipid excipients, and microbiome-responsive carriers are drawing interest for interacting with gut bacteria to improve absorption and reduce variability. Organ-on-a-chip systems offer more realistic human-based predictions of pharmacokinetic behavior than older cell cultures or animal testing, and exosome-inspired lipid carriers mimic natural exosomes with strong biocompatibility and tailorable targeting.

Still, despite this progress, clinical translation remains limited, and moving forward will require standardized characterization methods, biorelevant dissolution testing, validated IVIVC models, solutions to manufacturing scale-up, and well-designed Phase I trials demonstrating better pharmacokinetics than what already exists on the market.

17. CONCLUSION

This review worked through the range of lipid-based nanocarrier approaches explored to improve telmisartan's oral bioavailability and therapeutic performance. Every major category, SLNs, NLCs, SNEDDS, nanoemulsions, liposomes, niosomes, cubosomes, phytosomes, and LPHNPs, delivers measurable bioavailability gains, with preclinical AUC improvements ranging from 2.4-fold for phytosomes to 5.1-fold for LPHNPs. The degree of improvement depends less on which carrier type is chosen and more on formulation optimization, excipient selection, manufacturing control, and the physical state of the drug within the carrier. QbD frameworks now offer a workable, regulator-friendly path for formulation development, and these carriers are moving beyond simple bioavailability enhancement into precision-medicine territory through supersaturable SNEDDS, stimulus-responsive systems, co-delivery formulations, AI-assisted design, 3D printing, and organ-targeted delivery.

The main gap left to close is turning strong preclinical results into approved products, which will take sustained collaboration across formulation scientists, pharmacokineticists, regulatory experts, and manufacturing engineers meeting today's rigorous regulatory standards.

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