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Nanostructured Lipid Carriers for Oral Antihypertensive Drug Delivery: Overcoming Bioavailability Barriers for Enhanced Therapeutic Efficacy.

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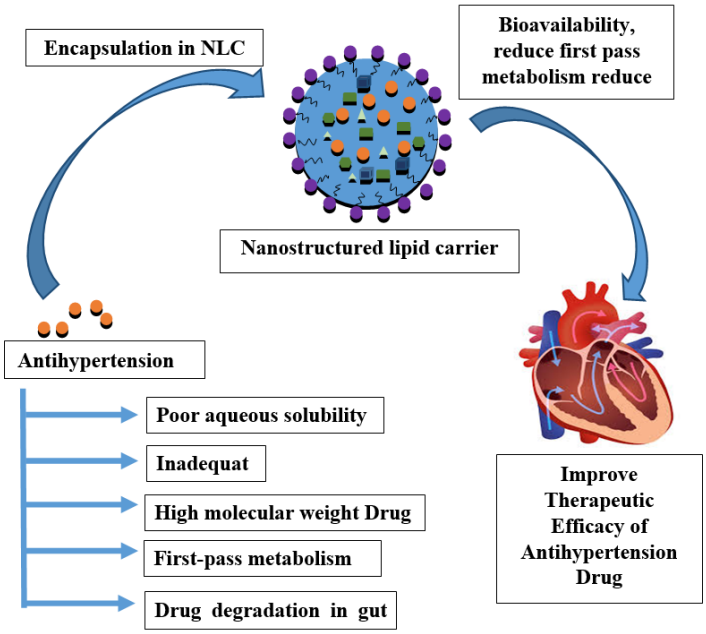
ABSTRACT
Despite the availability of many hypertensive medications, only about 14% of people with arterial hypertension have their blood pressure under control, despite the fact that there are billions of people with this condition worldwide. Poor bioavailability is a critical factor that negatively affects the efficacy of available treatment, resulting in increased dosing requirements that can cause more side effects and patient noncompliance. Lipid-based colloidal systems, including solid lipid nano carriers, nanostructure lipid carriers, nano-capsules, liposomes, and micro emulsion, are the current and important delivery systems for drug development and for improving the solubility and bioavailability of antihypertensive drugs. The second generation of lipid nano carriers, known as nanostructured lipids (NLCs), overcome the limitations of solid lipid nanoparticles (SLNs) by using biodegradable and compatible lipids (solid lipid –liquid lipid) and emulsifiers. The incorporation of liquid lipids results in structural imperfections in solid lipids, which results in a less ordered arrangement that reduces drug leakage and improves drug loading. This article summarizes the specifics of the nanostructure lipid carrier system.

Graphical Abstract:



Journal of Molecular Science
Journal of Molecular Science
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INTRODUCTION:

Hypertension is a major global health concern and a leading risk factor for cardiovascular diseases (CVDs) such as heart failure, coronary artery disease, myocardial infarction, and stroke [1]. Early stages are often asymptomatic, but untreated cases significantly increase morbidity and mortality. Current first-line antihypertensive agents diuretics, ACE inhibitors, angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCBs) are effective but face limitations including low bioavailability, frequent dosing, side effects, and poor patient compliance [2]. Diuretics remain widely used but may cause glucose fluctuation, hypokalaemia, and dehydration. ACE inhibitors reduce cardiovascular remodelling but require optimisation of efficacy and tolerability. ARBs, though well tolerated, suffer from low absorption and high dose requirements [3]. Many CCBs are poorly water-soluble and undergo extensive first-pass metabolism, necessitating higher doses [4]. Nanotechnology-based delivery systems offer promising solutions. First-generation solid lipid nanoparticles (SLNs), introduced in the 1990s, improved drug stability and used biocompatible lipids but had drawbacks like low drug loading and instability during storage [5]. Second-generation nanostructured lipid carriers (NLCs) combine solid and liquid lipids, enhancing drug loading, reducing leakage, improving stability, and enabling controlled release. NLCs are versatile for oral, parenteral, and topical delivery, showing potential to overcome shortcomings of conventional oral antihypertensive formulations [6].

Hypertension:

Hypertension is a chronic disorder with no definitive cure, but its onset and complications can be minimized by addressing modifiable risk factors such as excessive salt and fat intake, low potassium levels, obesity, physical inactivity, and alcohol overconsumption. Lifestyle modifications dietary adjustments, weight management, and increased physical activity are the first-line approach to reducing blood pressure (BP) [7]. However, if optimal BP is not achieved, pharmacological intervention becomes necessary. Several antihypertensive agents suffer from poor oral bioavailability due to factors such as extensive first-pass metabolism, low solubility, or limited permeability. Table 1 summarizes representative drugs from different antihypertensive classes along with their pharmacokinetic properties, metabolism, and common adverse effects [8].

Classification of Antihypertensive Agents [9, 10]

Diuretics: Thiazide diuretics (e.g., hydrochlorothiazide, chlortalidone) remain first-line due to their efficacy in reducing BP and cardiovascular risk. They act in the distal tubule to inhibit sodium and chloride reabsorption, leading to diuresis and reduced plasma volume.

Adrenergic Inhibitors: Beta-blockers (atenolol, metoprolol) decrease heart rate and cardiac output by blocking β-receptors; alpha-blockers (prazosin, terazosin) promote vasodilation and reduce peripheral resistance.

ACE Inhibitors: Preferred in patients <55 years and in those with heart failure, diabetic nephropathy, or chronic kidney disease; they reduce cardiovascular remodelling and protect renal function.

ARBs: (losartan, telmisartan) block angiotensin II receptors in vascular and cardiac tissue; often prescribed when ACEIs are not tolerated.

Direct-Acting Sympatholytics: (methyldopa, clonidine) suppress sympathetic nerve activity by acting on the CNS vasomotor centre.

Calcium Channel Blockers: Dihydropyridines (amlodipine) cause arterial vasodilation; non-dihydropyridines (verapamil, diltiazem) additionally reduce cardiac conduction.

Vasodilators: (hydralazine, minoxidil) relax vascular smooth muscle, usually reserved for resistant hypertension.

Table 1. Some Antihypertensive Drugs with Poor Bioavailability [11-16]

Sr. No.	Drug	Therapeutic Dose (mg)	Frequency/ Day	Bioavailability (%)	Drug Metabolism	Half-Life (hrs)	Adverse Effects
1	Valsartan	80–320	1	25	Hepatic	6	Diarrhea, hypotension, tiredness, bradycardia, dizziness
2	Losartan	50–100	1–2	25–35	Hepatic	1.5–2.5	Tachycardia, swelling of lips and feet, heaviness of legs

Journal of Molecular Science
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Volume 35 Issue 3, Year of Publication 2025, Page 563-570
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3	Candesartan	8–32	1	15	Hepatic, intestinal	9	Cough, stomach/joint pain, diarrhea, headache
4	Olmesartan	2.5–160	1	26	Hepatic	15	UTI, edema (legs, ankles, feet), nausea, dizziness
5	Nimodipine	30	1	13	Hepatic	7–9	Stomach bloating, severe abdominal pain
6	Nicardipine	60–120	1–2	35	Hepatic	8.6	Headache, flushing, dizziness, muscle cramps, tiredness
7	Nifedipine	30–120	1–2	45–68	CYP3A4 (Hepatic)	2	Headache, flushing, constipation, muscle cramps, tiredness
8	Isradipine	2.5–10	1	15–24	Hepatic	8	Headache, dizziness, ankle/leg edema
9	Felodipine	2.5–10	1	15	Hepatic	25	Headache, flushing, dizziness, tiredness
10	Enalapril	5–40	1–2	40–60	None	11–14	Cough, headache, vomiting, diarrhea, itching, blurred vision
11	Ramipril	2.5–20	1	28	Hepatic	2–4	Cough, headache, vomiting, diarrhea, itching, blurred vision
12	Lisinopril	10–40	1	25	None	12	Cough, headache, vomiting, diarrhea, itching, blurred vision
13	Diltiazem	180–480	1–2	40	Hepatic	3–4.5	Edema (head, ankles, feet), headache, dizziness, tiredness
14	Verapamil	120–480	1–2	20–30	Hepatic	2.8–7.4	Dizziness, tiredness, bradycardia, constipation
15	Acebutolol	200–1200	1	40	Hepatic	3–4	Dizziness, tiredness, bradycardia, constipation, muscle pain
16	Nebivolol	2.5–10	1	12–98	Hepatic	11–40	Weight changes, tingling in feet
17	Carvedilol	12.5–50	1–2	25–35	Hepatic	7–10	Dizziness, tiredness, bradycardia, nausea, vomiting, muscle pain
18	Atenolol	25–100	1–2	50	Hepatic	6–9	Hypotension, dizziness, tiredness, bradycardia, nausea, muscle pain
19	Propranolol	40–240	2–3	26	Hepatic	2–4	Dizziness, tiredness, bradycardia, cold extremities, nightmares, muscle pain
20	Furosemide	20–480	2–3	60–65	Hepatic	4	Vertigo, blurred vision, stomach cramps, headache
21	Methyldopa	500–2250	2–3	25	Hepatic	1.5–2	Dizziness, tiredness, bradycardia, nausea, vomiting
22	Prazosin	0.5–20	2–3	55–82	Hepatic	1–3	Drowsiness, dizziness, tiredness, palpitations, constipation, muscle pain
23	Doxazosin	0.5–16	1	62–69	Hepatic	16–22	Vertigo, edema (ankles, feet, fingers), abdominal pain, headache

Limitations of Oral Antihypertensive Agents:
Poor Aqueous Solubility: Common in BCS Class II and IV drugs, leading to dissolution-limited absorption and reduced systemic exposure [17].

Low Lipophilicity: Drugs outside the optimal log P range (1–3) exhibit poor membrane permeability, hindering passive absorption [18].

High Molecular Weight: Larger molecules face difficulty crossing lipid membranes, limiting oral absorption.

First-Pass Metabolism: – Significant pre-systemic metabolism in the gut and liver reduces plasma concentration to <50% of the administered dose [18].

Gastrointestinal Degradation: Acidic pH and digestive enzymes cause chemical and enzymatic breakdown, lowering systemic availability [19].

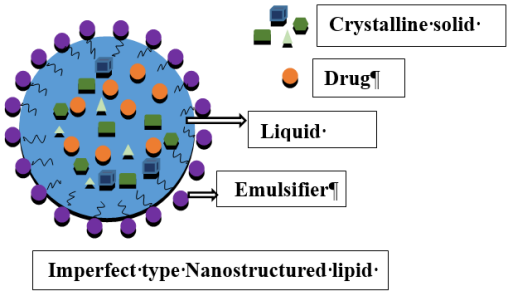
Nanostructured Lipid Carriers (NLCs):
An effective drug delivery system must ensure safe, efficient, and targeted transport of therapeutic agents. While several carriers liposomes, nanoemulsions, polymeric nanoparticles have been explored, challenges such as poor physiological

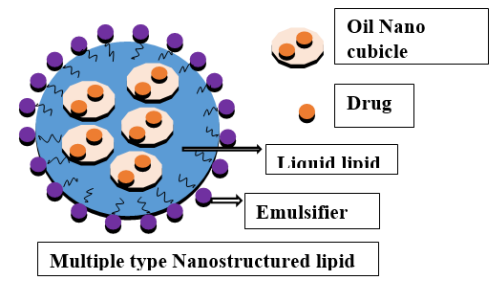
Journal of Molecular Science
Volume 35 Issue 3, Year of Publication 2025, Page 563-570
DoI-10.004687/1000-9035.2025.077

stability, limited drug loading, and high production costs persist [20]. Solid lipid nanoparticles (SLNs), introduced by Müller et al., improved stability and biocompatibility but suffered from low drug-loading capacity, burst release, and storage-related drug leakage. To address these drawbacks, second-generation NLCs were developed, combining solid and liquid lipids to create structural imperfections within the lipid matrix. This design increases drug loading, minimizes leakage, and enhances stability while retaining the safety and biodegradability of lipid systems. NLCs also merge the benefits of liposomes, nanoemulsions, and SLNs, making them suitable for lipophilic and hydrophilic drugs across oral, topical, and parenteral routes [21].

Structure and Types of NLCs:
NLCs are formed by mixing spatially incompatible solid and liquid lipids, resulting in small oil compartments within a solid crystalline matrix [22]. Depending on lipid arrangement and production method, NLCs are classified as [Figure 2]:

- **Imperfect-Type NLCs** – Use diverse lipids (e.g., glycerides) to create a highly disordered matrix with more empty spaces for drug accommodation.
- **Multiple-Type NLCs** – Contain oil droplets dispersed within a solid lipid phase, improving solubility for lipophilic drugs.
- **Amorphous-Type NLCs** – Maintain a non-crystalline, structure-less lipid matrix to prevent drug expulsion during storage.





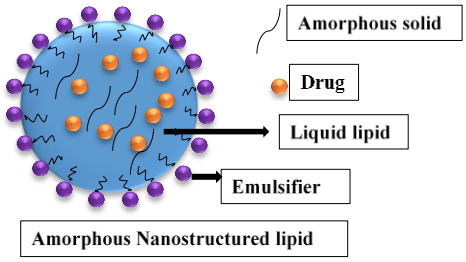


Figure 2: NLCs Classification Based on the lipid matrix structure

Composition of NLCs
Lipids: Solid lipids include triglycerides (tripalmitin, tristearin), partial glycerides (compritol® 888 ATO), fatty acids (stearic, palmitic acid), waxes, and sterols. Liquid lipids are unsaturated mono-, di-, and triglycerides with varying chain lengths. The solid/liquid lipid ratio (typically 70:30 to 99:0.1) affects particle size and drug-loading capacity [22].

Surfactants: Surfactants stabilize NLCs by reducing interfacial tension. Examples include hydrophilic (poloxamer 188, Tween 80), lipophilic (Span 20, Span 80), cationic (alkyl amines, ammoniums), and non-ionic types (polysorbates). Non-ionic surfactants are generally safer and less irritating [23].

Methods of Preparation of Nanostructured Lipid Carriers (NLCs):
High-Energy Methods:
Hot High-Pressure Homogenization (Hot-HPH)
In this method, the drug is mixed with solid and liquid lipids, and the mixture is melted at 5–10 °C above the solid lipid's melting point [Figure 3]. This melt is dispersed in a hot aqueous surfactant solution of the same temperature to form a hot pre-emulsion using high-shear mixing (100–2000 bar). High-pressure homogenization produces a fine oil-in-water emulsion, which recrystallizes into NLCs upon cooling [24].

Cold High-Pressure Homogenization (Cold-HPH)
Here, the melted lipid–drug mixture is rapidly cooled using liquid nitrogen, then ground into microparticles. These are dispersed in a cold surfactant solution and homogenized at high pressure (5–10 cycles at ~1500 bar). Cold-HPH avoids thermal degradation of thermolabile drugs and is highly reproducible, solvent-free, scalable, and suitable for large-scale manufacturing [25].

High-Shear Homogenization / Ultrasonication:
Similar to Hot-HPH, but after forming the hot pre-emulsion, ultrasonication is used instead of high-pressure homogenization. This technique requires less complex equipment and minimal surfactants,

Journal of Molecular Science
Volume 35 Issue 3, Year of Publication 2025, Page 563-570
DoI-10.004687/1000-9035.2025.077

but has a risk of metal contamination from probe tips and still requires significant energy input [26].

Melt Emulsification Homogenization:
Solid and liquid lipids with the drug are dispersed in an aqueous surfactant solution, subjected to probe sonication, and cooled to form NLCs. This method is simple but may yield a broader particle size distribution [27].

Low-Energy Methods:
Microemulsion Method:
Molten lipids containing the drug are mixed with a warm aqueous surfactant solution to form a microemulsion. This is quickly dispersed into ice-cold water (20–50× the microemulsion volume), causing lipid precipitation as NLCs. Advantages include simplicity, reproducibility, and solvent-free processing, but it requires high surfactant concentrations and large water volumes [28].

Double Emulsion Method (w/o/w):
An aqueous drug solution is emulsified into molten lipid (w/o) and then re-emulsified into an external aqueous surfactant solution (w/o/w) at 2–3 °C. Ultrafiltration is used for purification. This technique improves encapsulation of hydrophilic drugs, but involves multiple emulsification steps and sophisticated equipment [29].

Membrane Contractor Method:
Molten lipid is pressed through a porous membrane into a cold aqueous surfactant phase. Lipid droplets solidify into NLCs upon cooling. Particle size depends on membrane pore size, lipid temperature, and applied pressure. The method is precise but technically demanding [30].

Phase Inversion Method:
A water-in-oil (w/o) emulsion of lipids, water, and surfactants at high temperature is inverted to oil-in-water (o/w) by adding cold water under constant stirring, leading to lipid recrystallization into NLCs. This solvent-free and scalable method is suitable for thermolabile drugs [31].

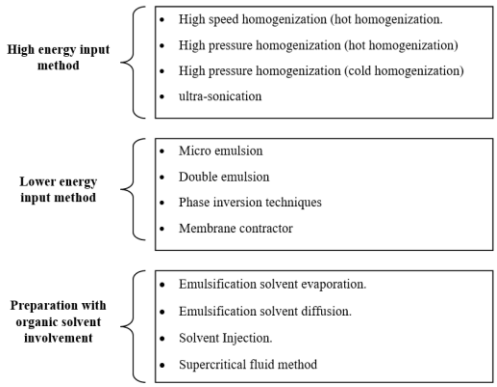


Figure 3: Preparation Methods for Nanostructured Lipid Carrier [32]

Organic Solvent Methods:
Emulsification–Solvent Evaporation:
Lipids and drug are dissolved in a water-immiscible organic solvent (e.g., chloroform, dichloromethane, DMSO). This solution is emulsified in an aqueous surfactant phase, and the solvent is evaporated to form NLCs. The method is ideal for thermolabile drugs but requires complete removal of toxic solvents [33].

Emulsification–Solvent Diffusion:
Lipids and drug are dissolved in partially water-miscible solvents (e.g., methanol, ethanol, acetone). Pre-saturation with water is followed by emulsification in an aqueous phase, allowing solvent diffusion and lipid solidification into NLCs [34].

Solvent Injection:
Melted lipids in a solvent are injected through a membrane into an aqueous phase, forming lipid droplets that solidify into NLCs upon cooling. Particle size is influenced by injection pressure, membrane pore size, and phase temperatures [35].

Supercritical Fluid Method:
Lipids and drug are dissolved in an organic solvent and emulsified in water. Supercritical CO_2 is introduced to precipitate nanoparticles. This method offers solvent-free final products but requires specialized high-pressure equipment [36].

Characterization of Nanostructured Lipid Carriers (NLCs):
Particle Size Analysis:
Particle size is a crucial determinant of NLC absorption**,** biodistribution, and clearance. For orally administered NLCs, smaller particles (<300 nm) exhibit enhanced gastrointestinal transit and are less prone to elimination by the reticuloendothelial system [37]. Two primary analytical techniques are employed:

- **Photon Correlation Spectroscopy (PCS):** Offers high sensitivity and precision for particles from a few nanometers up to ~3 µm. Particularly useful for assessing nanoscale formulations, but less accurate for larger particles.
- **Laser Diffraction:** Measures particle sizes based on the correlation between diffraction angle and particle radius; smaller particles scatter light at higher angles. Effective for detecting a broad size range but less sensitive to very small nanoparticles.

Polydispersity Index (PDI):
PDI reflects the uniformity of particle size distribution. Lower PDI values indicate higher

Journal of Molecular Science
Volume 35 Issue 3, Year of Publication 2025, Page 563-570
DoI-10.004687/1000-9035.2025.077

monodispersity and improved formulation stability. A PDI value <0.3 is generally considered optimal. PDI is commonly determined using PCS**,** which measures fluctuations in scattered light intensity to assess particle size variability [38].

Zeta Potential (ZP):
Zeta potential measures the surface charge of nanoparticles, which influences colloidal stability. High absolute ZP values (±30 mV or greater) enhance electrostatic repulsion, preventing particle aggregation. Low ZP values increase the likelihood of flocculation or coagulation, adversely affecting stability. ZP measurements are typically performed using PCS [39].

Morphological Analysis:
Microscopy techniques provide visual confirmation of shape**,** surface texture, and size distribution [40]:

- **Atomic Force Microscopy (AFM):** Delivers topographical maps at nanometer resolution.
- **Transmission Electron Microscopy (TEM):** Uses transmitted electrons to reveal internal structure and shape.
- **Scanning Electron Microscopy (SEM):** Uses surface-scattered electrons to show surface morphology.

Crystallinity and Polymorphism:
The physical state of lipids impacts drug loading, stability, and release [41].

- **X-ray Diffraction (XRD):** Identifies crystalline structures and degree of crystallinity.
- **Differential Scanning Calorimetry (DSC):** Detects melting transitions and assesses polymorphic forms.

Entrapment Efficiency:
Entrapment efficiency (EE%) evaluates the proportion of drug successfully incorporated within the NLC matrix [42].

***In-Vitro* Drug Release Studies:**
These studies assess release kinetics under controlled conditions, often using a dialysis bag method [43]:

Drug–Lipid Interaction:
Fourier Transform Infrared Spectroscopy (FTIR) is used to detect potential chemical interactions between drug and lipid components [44].

In Vivo Studies:
Pharmacokinetic studies measure AUC, Cmax, and Tmax to determine absorption and bioavailability. Pharmacodynamic studies assess therapeutic efficacy in animal models, comparing NLC formulations to pure drug or conventional delivery systems [45].

Stability Studies:

- **Real-Time Stability** – Storage at 30 ± 2 °C for 30 days; periodic evaluation of pH**,** particle size**,** PDI, and organoleptic properties [46].
- **Freeze–Thaw Stability** – Storage at 4 ± 2 °C for 24 h (one cycle), alternating with thawing; repeated up to six cycles (12 days) to test resilience against temperature stress [47].

Application of Nanostructured Lipid Carriers (NLCs):
Therapeutic efficacy of many antihypertensive drugs is limited by their poor bioavailability, primarily due to low solubility, extensive hepatic first-pass metabolism, P-glycoprotein (P-gp) efflux, and susceptibility to enzymatic or chemical degradation [48]. These factors result in suboptimal plasma concentrations, necessitating frequent dosing and increasing the risk of poor blood pressure control and cardiovascular events. Oral delivery remains the most common and patient-friendly route; however, these intrinsic barriers significantly reduce the clinical effectiveness of many antihypertensive agents [49]. NLCs provide a promising approach to overcome these challenges. By encapsulating antihypertensive drugs within a lipid matrix, NLCs enhance solubility, improve intestinal absorption, protect drugs from degradation, and offer sustained drug release thereby maintaining therapeutic plasma levels for prolonged periods [50]. The high surface area and saturation solubility of nanoparticles accelerate onset of action, while the lipids and surfactants used can inhibit P-gp efflux, further improving absorption. Additionally, NLCs can facilitate lymphatic transport, bypassing hepatic metabolism and increasing systemic bioavailability [51].

Conclusion and Future Perspectives:
Many cutting-edge nanoscale drug delivery techniques are being extensively studied at both laboratory and industrial sizes in the field of pharmaceutical research and development today. Drug delivery systems at the nanoscale offer a robust stability profile for both drug and carrier systems, which makes them perfect for developing dosages. NLCs are the newest and most sophisticated NLC formulations, offering improved pharmacological efficacy, more flexibility in drug loading, and the ability to manipulate release patterns. The low water solubility of the medications created during drug development continues to worry pharmaceutical specialists. These substances have a high first-pass metabolism, weak permeability, and substantial ex vivo bioavailability. GIT instability and toxicity issues. Lipid nanoparticles' capacity to retain significant amounts of bioactive substances, delay

Journal of Molecular Science
Volume 35 Issue 3, Year of Publication 2025, Page 563-570
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their premature breakdown, and boost their oral bioavailability has been investigated by researchers. By rupturing the intestinal membrane, the surfactants utilized in NLC formulations can enhance drug penetration and stop P-gp efflux. Improved pharmacokinetic characteristics of drug-loaded NLCs suggest that they may be able to control the release of encapsulated medications and increase therapeutic efficacy. Researchers have suggested adjusting the physical characteristics of modified NLCs by altering their compositions in order to maximize their potential, and the manufacturing process may produce encouraging outcomes.

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