Liver-Targeted Nanoparticle-Based Delivery Systems for Hepatitis C Therapy: Current Advances, Translational Barriers, and Future Perspectives

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Abstract

Background:
Hepatitis C virus infection remains a major cause of chronic liver disease, fibrosis, cirrhosis, and hepatocellular carcinoma worldwide. Although direct-acting antivirals have greatly improved cure rates, several clinical challenges remain, including drug resistance, reinfection, poor access to therapy, drug–drug interactions, advanced liver disease, and post-treatment liver complications. These limitations create a need for improved liver-specific therapeutic strategies.

Purpose:
The purpose of this review is to critically examine liver-targeted nanoparticle-based delivery systems for hepatitis C therapy, with emphasis on their mechanisms, advantages, limitations, translational challenges, and future potential in improving antiviral delivery and liver-specific treatment outcomes.

Methods:
This review synthesizes published scientific literature on hepatitis C virus biology, current antiviral therapies, liver-targeted drug delivery, and nanoparticle-based systems including liposomes, solid lipid nanoparticles, polymeric nanoparticles, micelles, dendrimers, inorganic nanoparticles, lipid nanoparticles, exosomes, and biomimetic carriers. Special attention is given to hepatocyte-specific targeting receptors such as ASGPR, LDL receptor, scavenger receptors, mannose receptors, and bile acid transporters.

Findings:
Nanoparticle-based delivery systems offer several potential advantages for hepatitis C therapy, including improved hepatic drug accumulation, reduced systemic toxicity, enhanced solubility of poorly water-soluble antivirals, protection of unstable nucleic acid therapeutics, controlled drug release, and the possibility of combination delivery. These systems may be particularly useful for delivering siRNA, miRNA modulators, antisense oligonucleotides, CRISPR-based tools, immunomodulators, and multifunctional antiviral–antifibrotic therapies. However, most HCV-related nanoparticle systems remain preclinical due to challenges in safety, reproducibility, scale-up, regulatory approval, cost-effectiveness, and competition with highly effective oral direct-acting antivirals.

Conclusion:
Liver-targeted nanoparticle-based delivery systems should be viewed as complementary strategies rather than replacements for existing direct-acting antivirals. Their greatest future value may lie in difficult-to-treat populations, drug-resistant infection, advanced liver disease, post-SVR liver complications, and nucleic acid-based therapies. Future research should focus on clinically realistic, disease-stage-specific, safe, scalable, and affordable nanomedicine platforms for precision hepatology.

Keywords: Hepatitis C virus; liver targeting; nanoparticles; direct-acting antivirals; hepatocytes; lipid nanoparticles; siRNA delivery; nanomedicine.

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1. Background:

Hepatitis C virus is an enveloped positive-sense RNA virus with a strong tropism for the liver. Since its identification in 1989 as the principal agent of non-A, non-B hepatitis, HCV has become one of the most intensively studied hepatotropic viruses. The initial discovery enabled serological screening, molecular diagnostics, and eventually rational antiviral development. Historical accounts of the discovery emphasize that cloning of the viral genome in 1989 transformed both transfusion safety and viral hepatitis research. [1-4]

The clinical significance of HCV lies not only in acute infection but in its ability to establish chronic infection. Persistent viral replication drives hepatic inflammation, progressive fibrosis, cirrhosis, and in some patients hepatocellular carcinoma. WHO estimated that in 2022 around 242,000 people died from hepatitis C, largely because of cirrhosis and hepatocellular carcinoma. This burden is unevenly distributed, with diagnosis and treatment access remaining major barriers in many regions.[5,6]

Therapy for HCV has undergone a striking evolution. Interferon and ribavirin were once the backbone of treatment, but they required long courses, produced frequent systemic adverse effects, and delivered variable response rates depending on genotype and host factors. The introduction of direct-acting antivirals changed the field fundamentally. Current DAA combinations target viral proteins such as NS3/4A protease, NS5A, and NS5B polymerase. Modern regimens are oral, short-duration, well tolerated, and highly effective, with cure rates commonly exceeding 95% in treated patients. [7-11]

Yet a high cure rate does not mean the therapeutic problem has disappeared. Several gaps remain. Patients with decompensated cirrhosis require careful regimen selection. Resistance-associated substitutions may complicate retreatment. Reinfection remains relevant in high-risk populations. Drug–drug interactions matter in patients receiving antiretrovirals, immunosuppressants, antiepileptics, anticoagulants, or complex polypharmacy. Post-SVR patients with advanced fibrosis or cirrhosis remain at risk for hepatocellular carcinoma. Access and affordability also continue to limit the public health impact of DAAs in several settings. WHO notes that access to diagnosis and treatment remains low despite the high efficacy of DAAs. [12-16]

In this context, liver-targeted nanoparticle delivery should not be positioned as a competitor to oral DAAs. A more realistic and scientifically useful framing is to view nanocarriers as adjunctive or enabling technologies. They may improve delivery of poorly soluble antivirals, reduce systemic toxicity of older agents, deliver nucleic acid therapeutics such as siRNA, antisense oligonucleotides, miRNA modulators, or CRISPR-based systems, and combine antiviral activity with antifibrotic or anti-inflammatory support.

The liver is particularly suited to nanomedicine because of its vascular architecture, sinusoidal fenestrations, resident macrophages, abundant hepatocytes, and high expression of uptake receptors. Passive liver accumulation can occur through the reticuloendothelial system, whereas active targeting can be achieved through receptors such as ASGPR, LDL receptor, scavenger receptors, mannose receptors, and bile acid transporters. GalNAc-mediated ASGPR targeting is especially important because ASGPR is highly expressed in hepatocytes and supports receptor-mediated internalization.

Table 1. Evolution of HCV Therapy

Therapeutic approach	Mechanism	Advantages	Limitations	Relevance to nanoparticle delivery
Interferon monotherapy	Stimulates antiviral immune responses	First systemic antiviral option	Low response, high toxicity, long treatment	Nanocarriers may reduce systemic exposure

Pegylated interferon	Longer-acting immune modulation	Improved dosing over standard interferon	Depression, cytopenia, flu-like effects	Potential liver-localized immunomodulation
Ribavirin	Nucleoside analogue with multiple antiviral effects	Improved response with interferon	Hemolytic anemia, teratogenicity	Liver-targeted delivery may reduce toxicity
First-generation DAAs	Direct viral enzyme inhibition	Higher antiviral potency	Resistance, genotype limits, toxicity	Nanocarriers may support combination delivery
Pangenotypic DAAs	NS3/4A, NS5A, NS5B targeting	Short-course oral cure in most patients	Resistance, access gaps, drug interactions	Nanocarriers useful mainly in selected contexts
RNA/host-targeted therapies	Target viral RNA or host dependency factors	New mechanism, useful for resistance	Delivery and safety barriers	Strong rationale for LNPs, GalNAc, polymers

1.1 Hepatitis C Virus Biology and Therapeutic Targets

HCV belongs to the family *Flaviviridae* and carries a single-stranded positive-sense RNA genome. The viral genome encodes one large polyprotein that is cleaved into structural and non-structural proteins. Structural proteins include core and envelope glycoproteins E1 and E2, whereas non-structural proteins include p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B. These proteins coordinate entry, replication, assembly, and release.[17-19]

HCV entry is a multistep process involving attachment to hepatocyte-associated factors followed by receptor-mediated internalization. Several host factors contribute, including CD81, scavenger receptor class B type I, claudin-1, occludin, and lipoprotein-associated pathways. Viral entry is closely linked with lipid metabolism, which partly explains why hepatocyte biology is central to HCV infection.[18]

After entry and uncoating, the viral RNA is translated at the rough endoplasmic reticulum. The resulting polyprotein is processed by host and viral proteases. Replication occurs in rearranged intracellular membranes often described as the membranous web. NS5B functions as the RNA-dependent RNA polymerase. NS5A is a multifunctional phosphoprotein involved in replication complex formation and virion assembly. NS3/4A protease cleaves the viral polyprotein and also interferes with innate immune signaling pathways.[17,20-24]

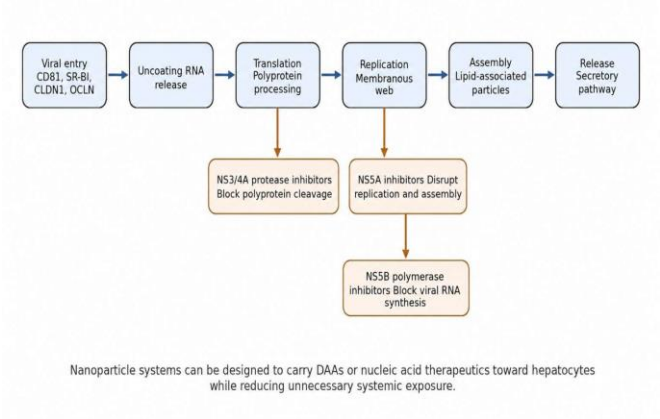

Figure 1: HCV life cycle and major antiviral targets relevant to direct-acting antiviral and nanoparticle-based delivery strategies.

The three most important DAA target classes are mentioned in Table 2:

Table 2: Key Molecular Targets of Direct-Acting Antivirals in Hepatitis C Virus

Target	Therapeutic relevance
NS3/4A protease	Blocks viral polyprotein processing
NS5A	Disrupts replication complex formation and assembly
NS5B polymerase	Blocks viral RNA synthesis through nucleoside or non-nucleoside inhibition

DAA therapy exploits these vulnerable steps. A recent review describes four DAA classes based on mechanism and target, including NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors. [9,12,13]

Despite these clear targets, HCV therapy must account for viral diversity. HCV has multiple genotypes and a high mutation rate due to error-prone RNA replication. Resistance-associated substitutions may emerge under drug pressure, especially when adherence is poor, drug exposure is suboptimal, or baseline resistance exists. Reinfection is also possible because viral clearance does not generate sterilizing immunity.[12,19]

Advanced liver disease adds another layer of complexity. Cirrhosis alters hepatic blood flow, sinusoidal structure, transporter expression, immune function, and drug metabolism. These changes may affect both free drugs and nanoparticle systems. A nanocarrier designed for healthy hepatocytes may not behave identically in fibrotic or cirrhotic liver tissue. Therefore, disease-stage-specific design should become an explicit principle in future liver-targeted HCV nanomedicine.[5,6,13]

1.2 Current Therapeutic Landscape of Hepatitis C

The therapeutic history of HCV can be divided into three broad phases: interferon-based immune stimulation, interferon plus ribavirin combination therapy, and DAA-based targeted antiviral therapy.[7,8]

Interferon therapy attempted to enhance antiviral immunity rather than directly inhibit viral enzymes. Pegylated interferon improved pharmacokinetics but did not eliminate systemic toxicity. Adverse effects included flu-like symptoms, depression, cytopenias, thyroid dysfunction, and poor tolerability. Ribavirin improved response rates when combined with interferon but introduced hemolytic anemia, teratogenicity, and additional monitoring requirements.

Direct-acting antivirals transformed treatment by directly targeting viral replication machinery. DAA regimens are shorter, oral, more tolerable, and far more effective than interferon-based therapy. AASLD-IDSA guidance states that DAA regimens cure more than 95% of treated people. The 2023 guidance also recommends treating confirmed acute HCV infection similarly to chronic infection without waiting for spontaneous clearance. [10,11,13-16]

Although current DAA regimens have transformed the therapeutic landscape of HCV infection, several unresolved issues remain that require ongoing clinical attention and research. These key challenges and their implications are presented in Table

3.

Table 3: Current Limitations and Challenges of Direct-Acting Antiviral Therapy

Remaining gap	Why it matters
Resistance	Can complicate retreatment after DAA failure
Reinfection	Relevant in high-risk groups
Drug–drug interactions	Important in HIV coinfection, transplant recipients, and polypharmacy
Decompensated cirrhosis	Limits use of some protease inhibitor-containing regimens
Access gaps	Diagnosis and treatment remain low in many regions
Cost	Still relevant in some health systems
Post-SVR liver disease	HCC surveillance remains necessary in advanced fibrosis/cirrhosis
Special populations	Include renal disease, transplant recipients, children, pregnancy, and immunosuppression

A review on DAA-era management notes that retreatment after failure may require combinations across multiple DAA classes and consideration of resistance-associated substitutions. This is one area where nanotechnology could be considered—not to replace approved retreatment regimens, but to improve delivery of combination agents, host-targeted therapies, or adjunctive antifibrotic interventions.[12,13]

Nanoparticle systems may also help when the therapeutic cargo is not a conventional small molecule. Antisense oligonucleotides, siRNA, miRNA inhibitors, and CRISPR-based tools require protection from degradation, efficient cellular uptake, endosomal escape, and controlled biodistribution. These are classic delivery problems that nanomedicine is designed to address.[25-31]

2. Rationale for Liver-Targeted Nanoparticle Delivery

The liver is a natural target for nanoparticle delivery because of its anatomy and function. It receives dual blood supply from the portal vein and hepatic artery, has fenestrated sinusoidal endothelium, and contains specialized cell populations including hepatocytes, Kupffer cells, liver sinusoidal endothelial cells, and hepatic stellate cells. These features promote the accumulation and processing of circulating particles.[32-36]

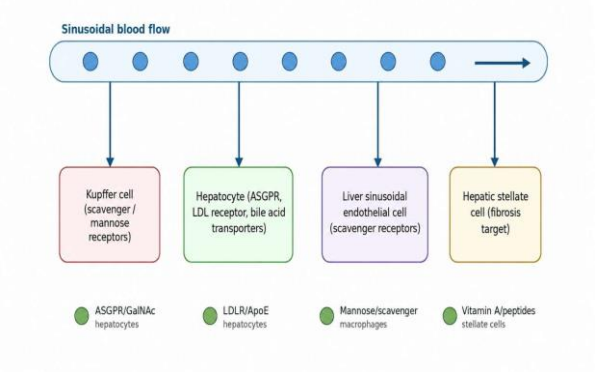

Figure 2: Simplified mechanism of liver-targeted nanoparticle delivery, showing passive sinusoidal accumulation and receptor-mediated uptake by hepatocytes and non-parenchymal liver cells.

Passive targeting occurs when nanoparticles are sequestered by the mononuclear phagocyte system, especially Kupffer cells. This can be useful when the therapeutic target is inflammatory macrophages, but it can be a limitation when hepatocyte delivery is required. Particle size, charge, surface hydrophobicity, protein corona formation, and PEGylation influence whether nanoparticles are cleared by Kupffer cells, retained in sinusoids, taken up by hepatocytes, or distributed extrahepatically.[26,27,30,31]

Active targeting attempts to redirect nanoparticles toward selected liver cell types. For hepatocytes, ASGPR is one of the most widely studied receptors. Galactose, lactose, N-acetylgalactosamine, and related ligands can promote ASGPR-mediated uptake. GalNAc-based delivery has become a major platform for liver-directed RNA therapeutics because ASGPR is highly expressed in hepatocytes and undergoes efficient recycling. [32-36]

Other targeting routes include LDL receptor-mediated uptake, bile acid transporter-mediated delivery, scavenger receptor pathways, mannose receptor targeting, and peptide-mediated strategies. Each route has advantages and limitations. LDL receptor targeting can exploit lipoprotein biology, which is relevant to HCV because the virus circulates partly as a lipoviroparticle. Bile acid transporter targeting may improve hepatobiliary delivery, but transporter expression may change in cholestasis or advanced liver disease. Mannose receptor targeting is more relevant to Kupffer cells and liver macrophages than hepatocytes.[36]

Nanotechnology-based drug delivery strategies offer significant opportunities for optimizing HCV treatment by improving pharmacokinetics, cellular targeting, and therapeutic outcomes. The major advantages of liver-targeted nanoparticles and their relevance to HCV therapy are summarized in Table 4.[25-31]

Table 4: Therapeutic Benefits of Liver-Targeted Nanoparticles for Hepatitis C Treatment

Advantage	Relevance to HCV therapy
Higher intrahepatic drug exposure	May improve local antiviral potency
Reduced systemic exposure	May lower toxicity
Protection of unstable cargo	Essential for RNA and protein therapeutics
Improved solubility	Useful for hydrophobic antivirals
Controlled release	May maintain therapeutic concentration
Combination delivery	Enables synchronized pharmacokinetics
Cellular targeting	Allows hepatocyte, macrophage, or stellate-cell-directed therapy

Multifunctionality	Enables antiviral plus antifibrotic or anti-inflammatory delivery

The strongest future rationale is not routine replacement of DAA tablets. Instead, it is targeted use in difficult therapeutic contexts: DAA resistance, advanced liver disease, post-SVR fibrosis, transplant recurrence risk, nucleic acid therapeutics, and combination regimens requiring coordinated delivery.

3. Types of Nanoparticle-Based Delivery Systems for HCV Therapy

3.1

Liposomes

Liposomes are phospholipid vesicles with aqueous cores and lipid bilayers. Hydrophilic drugs can be encapsulated in the aqueous compartment, whereas hydrophobic drugs can be incorporated into the lipid bilayer. Conventional liposomes are relatively biocompatible and can improve drug solubility and pharmacokinetics.[25]

For HCV therapy, liposomes are relevant for encapsulating antivirals, ribavirin, interferon-related molecules, immunomodulators, and nucleic acid cargos. PEGylated liposomes can prolong circulation time by reducing opsonization. Ligand-modified liposomes can be decorated with galactose, lactose, glycyrrhizin, peptides, antibodies, or other ligands to promote liver cell targeting.

Their limitations include leakage of encapsulated drug, instability during storage, immune recognition, complement activation, and manufacturing complexity. Liposomes may also accumulate in Kupffer cells rather than hepatocytes unless carefully engineered. For HCV, where hepatocytes are the primary infected cell type, surface targeting becomes especially important.

3.2 Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Solid lipid nanoparticles contain a solid lipid matrix that can incorporate lipophilic drugs and provide controlled release. Nanostructured lipid carriers improve upon SLNs by mixing solid and liquid lipids, creating imperfections in the lipid matrix that can increase drug loading.[37,38]

These systems are attractive for poorly soluble DAAs and other hydrophobic antivirals. They may improve oral absorption, lymphatic transport, hepatic exposure, and sustained release. Lipid-based carriers may also interact favorably with hepatic lipid metabolism, although this must be evaluated carefully.

Their limitations include polymorphic transitions of lipids, drug expulsion during storage, batch variability, and challenges in sterilization and scale-up. For HCV nanomedicine, SLNs and NLCs are promising only if they demonstrate a clear advantage over existing oral DAA formulations.

3.3 Polymeric Nanoparticles

Polymeric nanoparticles can be produced from biodegradable and synthetic polymers such as PLGA, chitosan, PEG-based copolymers, PEI, polycaprolactone, and dendritic polymers. PLGA is widely used because of biodegradability and regulatory familiarity. Chitosan offers mucoadhesive and cationic properties, making it useful for nucleic acid complexation. PEI supports endosomal escape but is limited by cytotoxicity.[39,40]

Polymeric nanoparticles can provide sustained release, protect labile cargo, and allow surface modification. In HCV therapy, they may deliver DAAs, ribavirin, siRNA, miRNA inhibitors, immunomodulators, or antifibrotic agents. Surface conjugation with GalNAc, galactose, glycyrrhizin, or peptides can increase hepatocyte targeting.

The main concerns are polymer toxicity, residual solvents, inflammatory responses, low nucleic acid release efficiency, and scale-up reproducibility. Cationic polymers are especially problematic because they can disrupt cell membranes and activate innate immunity.

3.4 Polymeric Micelles

Polymeric micelles are self-assembled nanostructures formed from amphiphilic block copolymers. They contain a hydrophobic core and hydrophilic shell. Their main strength is solubilization of hydrophobic drugs. This is

valuable for antiviral compounds with poor aqueous solubility.[41,42]

Micelles may passively accumulate in the liver and can be actively targeted through ligand conjugation. They can also be engineered for pH-sensitive or redox-sensitive release. However, micelles may dissociate upon dilution in blood, causing premature drug release. Stability depends on critical micelle concentration, polymer structure, and drug–core interactions.

For HCV therapy, micelles are most plausible as formulation enhancers for hydrophobic antivirals or combination therapy, rather than as primary platforms for RNA delivery.

3.5 Dendrimers

Dendrimers are highly branched, monodisperse macromolecules with multivalent surfaces. Their surface groups can bind drugs, nucleic acids, ligands, or imaging agents. This multivalency makes them attractive for antiviral therapy, receptor targeting, and gene delivery.[43]

Dendrimers may interact with viral particles or block viral entry, depending on surface chemistry. They can also complex nucleic acids and support endosomal escape. However, positively charged dendrimers can be cytotoxic, hemolytic, and immunostimulatory. Surface shielding or partial neutralization can reduce toxicity but may also reduce delivery efficiency.

Clinical translation of dendrimers for HCV therapy remains limited. Their future role may be in highly specialized delivery systems or topical/locoregional applications rather than systemic routine use.

3.6 Inorganic Nanoparticles

Inorganic nanoparticles include gold nanoparticles, silica nanoparticles, magnetic nanoparticles, quantum dots, and iron oxide systems. Their advantages include tunable size, optical or magnetic properties, imaging capability, and surface functionalization.[44-46]

Gold nanoparticles can support drug conjugation, biosensing, and photothermal strategies. Silica nanoparticles provide high surface area and pore volume. Magnetic nanoparticles can enable imaging or magnetically guided delivery. Quantum dots are more relevant to diagnostics and tracking than therapy because of toxicity concerns.

For HCV, inorganic nanoparticles may be more valuable in diagnostics, theranostics, biosensing, or mechanistic studies than in routine antiviral delivery. Long-term accumulation, poor biodegradability, and metal-associated toxicity remain major barriers.

3.7 Lipid Nanoparticles for RNA-Based Therapy

Lipid nanoparticles have become one of the most important delivery systems for nucleic acid therapeutics. They typically contain ionizable lipids, helper phospholipids, cholesterol, and PEG-lipids. Ionizable lipids are neutral at physiological pH but become protonated in acidic endosomes, promoting endosomal escape.[47-51]

LNPs are relevant to HCV because RNA-based strategies can target viral RNA, host dependency factors, miR-122 interactions, inflammatory pathways, or fibrogenic signaling. The approval of patisiran as an LNP-formulated siRNA drug demonstrated the clinical feasibility of systemic RNA delivery to the liver. [50,51]GalNAc-LNP systems are also being explored to improve hepatocyte specificity through ASGPR-mediated uptake. GalNAc targeting can reduce reliance on ApoE/LDLR-mediated uptake and may produce more hepatocyte-specific delivery.

The barriers are substantial: endosomal escape remains inefficient, innate immune activation must be controlled, repeated dosing can raise tolerability concerns, and manufacturing requires tight control of particle size, encapsulation efficiency, lipid composition, and impurities.

3.8 Exosomes and Biomimetic Nanocarriers

Exosomes are naturally secreted extracellular vesicles involved in intercellular communication. Their biological origin, membrane proteins, and potential tissue tropism make them attractive delivery vehicles. Biomimetic nanocarriers can also be produced by coating synthetic nanoparticles with cell membranes derived from hepatocytes, macrophages, platelets, or immune cells.[55,56]

For HCV-associated liver disease, exosomes and biomimetic carriers could deliver antiviral RNA, anti-inflammatory molecules, antifibrotic agents, or regenerative signals. Their natural membrane composition may reduce immune recognition and improve biological compatibility.

However, exosome translation is difficult. Isolation methods vary, loading efficiency is inconsistent, purity is challenging, and standardization remains unresolved. Exosomes may also carry unwanted biological signals. For HCV therapy, they remain scientifically exciting but clinically immature.

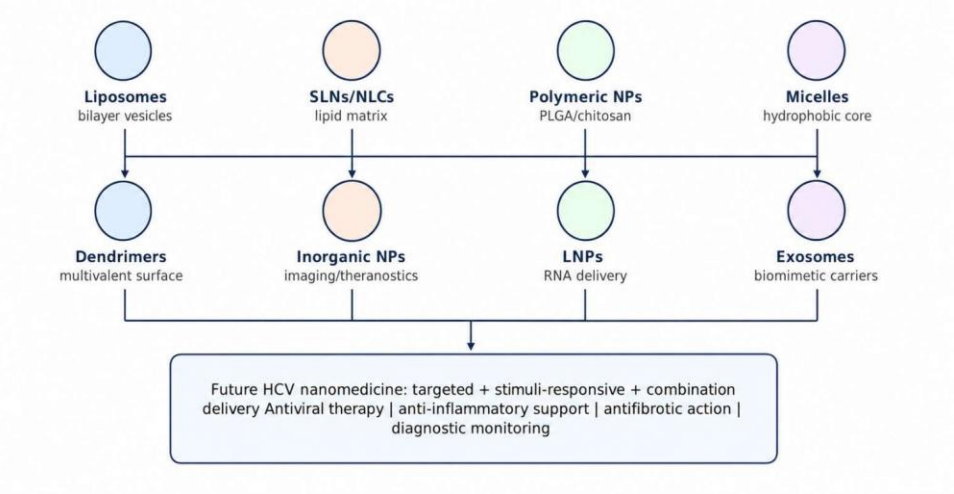

Figure 3: Simple overview of major nanoparticle platforms and the future concept of multifunctional liver-directed nanomedicine for HCV-associated liver disease.Table 5. Nanoparticle Systems Used for Liver-Targeted HCV Therapy

Nanoparticle type	Material used	Therapeutic cargo	Targeting strategy	Key advantages	Major limitations
Liposomes	Phospholipids, cholesterol	DAAs, ribavirin, interferon, RNA	Passive, PEGylated, ligand-modified	Biocompatible, versatile loading	Leakage, Kupffer uptake, instability
SLNs/NLCs	Solid/liquid lipids	Hydrophobic antivirals	Passive hepatic uptake, ligand modification	Solubility improvement, controlled release	Drug expulsion, polymorphism
Polymeric nanoparticles	PLGA, chitosan, PEG, PEI	DAAs, siRNA, miRNA inhibitors	ASGPR ligands, peptides	Sustained release, surface tunability	Toxicity, scale-up issues
Polymeric micelles	Amphiphilic block copolymers	Hydrophobic DAAs	Passive or ligand-based	Excellent solubilization	Dilution instability

Dendrimers	PAMAM and related polymers	Drugs, nucleic acids	Multivalent ligand display	High functional density	Cationic toxicity
Inorganic nanoparticles	Gold, silica, iron oxide	Drugs, imaging agents	Surface ligands, magnetic guidance	Theranostic potential	Long-term accumulation
Lipid nanoparticles	Ionizable lipids, cholesterol, PEG-lipid	siRNA, mRNA, ASO, CRISPR systems	ApoE/LDLR, GalNAc-ASGPR	Clinically validated RNA delivery	Endosomal escape, immune activation
Exosomes/biomimetic carriers	Natural vesicles, cell membranes	RNA, proteins, drugs	Native tropism, engineered ligands	Low immunogenicity potential	Standardization and purity problems

4. Liver-Targeting Strategies

4

.1 Passive Targeting to the Liver

Passive liver targeting is governed by nanoparticle physicochemical properties and hepatic clearance mechanisms. Larger particles and positively charged particles are more likely to be recognized by serum proteins and cleared by Kupffer cells. PEGylation can reduce opsonization but may also reduce cellular uptake. Particle size influences sinusoidal passage, macrophage capture, and hepatocyte access.[26,30,31]

In inflamed or fibrotic liver tissue, vascular permeability, extracellular matrix deposition, immune cell activity, and receptor expression may change. This means passive targeting is disease-stage dependent. A nanoparticle optimized in healthy animals may fail in cirrhotic liver because fibrosis alters sinusoidal fenestrations and hepatic perfusion.

4.2 Active Targeting to Hepatocytes

Active targeting uses ligands that bind hepatocyte receptors. The best-known strategy is ASGPR targeting using galactose, lactose, GalNAc, or related ligands. ASGPR is highly expressed in hepatocytes, supports rapid internalization, and recycles efficiently, making it a strong target for liver-directed delivery. [32-35]

LDL receptor targeting is also relevant because HCV interacts with lipoprotein metabolism. ApoE-containing particles can be taken up through LDL receptor family pathways. This is useful for some LNP systems but may be influenced by patient lipid status, liver disease, and competing endogenous lipoproteins.[18,36]

Bile acid transporter targeting uses bile acid conjugates to exploit hepatobiliary uptake pathways. Peptide-mediated targeting can offer specificity but requires careful validation to avoid off-target uptake.

The main limitation of active targeting is that receptor binding does not guarantee therapeutic delivery. Nanoparticles must still avoid premature clearance, reach

the target cell, undergo internalization, escape endosomes when needed, and release cargo in active form.

4.3 Targeting Non-Parenchymal Liver Cells

HCV primarily infects hepatocytes, but chronic HCV liver disease involves non-parenchymal cells. Kupffer cells contribute to inflammation. Hepatic stellate cells drive fibrosis. Liver sinusoidal endothelial cells regulate immune tolerance, vascular homeostasis, and sinusoidal structure.[17,18]

Targeting these cells may be valuable after viral clearance, especially in patients with persistent fibrosis or inflammation. For example, nanoparticles delivering antifibrotic siRNA or anti-inflammatory agents to stellate cells or macrophages could complement antiviral therapy. This supports the concept of multifunctional HCV nanomedicine: not only viral suppression, but also liver repair.

4.4 Stimuli-Responsive Targeting

Stimuli-responsive nanoparticles release cargo in response to local biological signals. Relevant triggers include acidic pH, high glutathione concentration, reactive oxygen species, disease-associated enzymes, and inflammatory mediators.[29]

In HCV-associated liver disease, oxidative stress, inflammation, and fibrosis create microenvironmental cues that could be exploited for selective release. ROS-responsive nanoparticles may release antioxidants or antifibrotic agents in inflamed tissue. Redox-sensitive carriers may release nucleic acids intracellularly. pH-sensitive systems may enhance endosomal escape.

The challenge is specificity. Many pathological triggers are not unique to HCV liver disease. Therefore, stimuli-responsive systems should be combined with cell-specific targeting and rigorous diseased-liver models.

Table 6. Liver-Targeting Ligands and Receptors

Target receptor/cell type	Ligand used	Targeted liver cell	Application in HCV therapy	Challenges
ASGPR	Galactose, lactose, GalNAc	Hepatocytes	DAA, siRNA, miRNA delivery	Receptor saturation, disease-stage variation
LDL receptor	ApoE, lipoprotein mimics	Hepatocytes	LNP uptake, lipoviroparticle-inspired delivery	Competition with endogenous lipoproteins
Scavenger receptors	Anionic ligands, modified lipids	Kupffer cells, endothelial cells	Immune modulation, inflammation targeting	Macrophage sequestration
Mannose receptor	Mannose	Kupffer cells/macrophages	Anti-inflammatory delivery	Limited hepatocyte specificity

Bile acid transporters	Bile acid conjugates	Hepatocytes	Hepatobiliary delivery	Altered expression in cholestasis
Stellate cell markers	Vitamin A, peptides	Hepatic stellate cells	Antifibrotic delivery	Activation-state dependency

1.5. Nanoparticle Delivery of Antiviral Agents

Nanoparticles can deliver several classes of therapeutic cargo relevant to HCV.

Direct-acting antivirals: Nanoparticles may improve solubility, hepatic concentration, and sustained release of DAAs. However, because oral DAAs are already highly effective, nanoparticle formulations must prove clear value in special situations such as poor solubility, drug interactions, resistance, or difficult tissue distribution.

Ribavirin: Ribavirin delivery through liver-targeted carriers could theoretically reduce systemic exposure and hemolytic toxicity. This is now less central because ribavirin use has declined, but it remains relevant in selected difficult-to-treat scenarios.

Interferon and immunomodulators: Nanocarriers may reduce systemic exposure and improve liver-localized immune modulation. However, broad immune activation risks inflammation, autoimmune toxicity, and poor tolerability.

siRNA and antisense oligonucleotides: RNA-based strategies can target viral RNA or host factors required for replication. miR-122 is especially important because HCV uses liver-specific miR-122 to stabilize and replicate its genome. Miravirsen, an antisense inhibitor of miR-122, demonstrated clinical antiviral activity, supporting host-targeted nucleic acid therapy as a viable concept. [47,52]

miRNA modulators: miR-122 inhibition can suppress HCV replication, but long-term modulation of a liver-enriched microRNA requires caution because miR-122 also regulates hepatic metabolism and tumor suppressive pathways. Later work has also shown that resistance mechanisms can emerge under miR-122-based pressure. [52-54]

CRISPR/Cas-based systems: Gene editing could theoretically target viral genomes or host dependency factors. Yet HCV is an RNA virus with high diversity, and permanent editing of host factors raises safety concerns. Delivery, off-target editing, immunogenicity, and ethical issues remain major barriers.

A realistic future approach may involve nanoparticles that co-deliver low-dose antiviral, anti-inflammatory, and antifibrotic agents in patients with advanced liver disease, rather than focusing only on viral clearance.

1.6. Preclinical and Clinical Advances

Preclinical HCV nanomedicine relies on multiple models, each with strengths and limitations. Huh7 and Huh7.5 hepatoma cells are commonly used because they support HCV replication systems, but they do not fully represent primary hepatocytes. Replicon systems are useful for studying viral RNA replication but do not capture the complete viral life cycle. HCV pseudoparticles help evaluate viral entry. Cell-culture-derived infectious HCV systems allow broader life-cycle studies but remain genotype-limited.[20-24]

Animal models are difficult because HCV has narrow species tropism. Humanized liver mouse models can support infection but are expensive, technically demanding, and immunologically imperfect. These limitations partly explain why many promising nanoparticle systems remain preclinical.

Organoids and liver-on-chip platforms may improve translation by modeling human hepatic architecture, multicellular interactions, fibrosis, inflammation, and flow conditions. These systems are particularly important for nanoparticles because static 2D cultures often fail to

predict biodistribution, protein corona formation, immune recognition, and tissue penetration.[57-60]

Clinical translation of HCV-specific nanoparticle therapies remains limited, largely because DAAs already work extremely well. Lessons from approved liver-targeted RNA therapeutics are therefore more relevant than direct HCV nanoparticle trials. Patisiran showed that LNP-mediated siRNA delivery to the liver can be clinically successful. GalNAc conjugates and GalNAc-modified nanoparticles further show how receptor-mediated liver targeting can be refined. [50,51]

1.7. Safety, Toxicity, and Biocompatibility Considerations

Safety is central to HCV nanomedicine because the target organ is often already injured. A nanoparticle tolerated by healthy liver may behave differently in chronic hepatitis, fibrosis, cirrhosis, steatosis, or cholestasis.[46,60]

Key toxicity issues and their mechanisms are presented in Table 7.

Table 7: Major Safety and Toxicity Concerns Associated with Nanoparticle-Based HCV Therapeutics

Toxicity issue	Mechanism
Hepatotoxicity	Direct hepatocyte stress or impaired mitochondrial function
Kupffer cell activation	Cytokine release and inflammatory amplification
Complement activation	Infusion reactions and hypersensitivity
Oxidative stress	ROS generation by particles or cargo
Long-term accumulation	Especially with inorganic or poorly degradable materials
Immunogenicity	Anti-PEG antibodies, innate immune activation, cytokine release
Hematological toxicity	Hemolysis, platelet activation, coagulation effects
Genotoxicity	Relevant for gene-editing and nucleic acid delivery

Diseased liver models are essential. Testing only in healthy animals can underestimate risk. Fibrotic livers have altered sinusoidal structure, macrophage activation, extracellular matrix deposition, and impaired clearance. Cirrhotic livers may show altered distribution and higher sensitivity to inflammatory insults.[57-60]

For RNA and gene-editing cargos, additional concerns include off-target gene silencing, immune activation through pattern-recognition receptors, unintended editing, persistence of editing machinery, and germline risk if biodistribution is not tightly controlled.

1.8 Major Challenges in Translation

The development of effective HCV nanotherapeutics requires overcoming several translational barriers related to formulation reproducibility, large-scale manufacturing, safety evaluation, and regulatory approval. These key challenges are summarized in Table 8.[26,30,31]

Table 8: Current Limitations in the Development of HCV Nanomedicine Platforms

Challenge	Explanation
Weak in vitro–in vivo correlation	Cell culture does not reproduce liver blood flow, immune clearance, or fibrosis
Batch variability	Nanoparticle properties are highly process-sensitive
Scale-up	Mixing, temperature, solvent removal, and sterilization affect quality
Stability	Aggregation, leakage, oxidation, and hydrolysis may occur
Regulatory uncertainty	Multifunctional systems are difficult to classify
Cost	Complex nanomedicines must compete with oral DAAs
Clinical trial design	Hard to justify trials where standard care is already highly effective
Commercial incentive	HCV cure rates reduce market need for new delivery systems
Safety expectations	Long-term liver safety must be strong

The most difficult question is not whether nanoparticles can deliver antivirals to the liver. The harder question is whether they can provide enough clinical advantage to justify added complexity. For routine uncomplicated HCV infection, the answer is probably no. For DAA failure, advanced liver disease, post-SVR fibrosis, transplant-related recurrence risk, and nucleic acid therapy, the answer may be different.

Table 9. Translational Challenges and Proposed Solutions

Challenge	Reason	Impact on clinical translation	Possible solution
Limited need in routine HCV	DAAs already cure most patients	Weak commercial rationale	Focus on resistant and advanced disease
Poor model predictivity	2D cells do not mimic diseased liver	Preclinical failure	Use organoids and liver-on-chip

Scale-up variability	Nanoparticles are process-sensitive	Batch inconsistency	Quality-by-design manufacturing
Toxicity in diseased liver	Fibrotic liver handles particles differently	Safety concerns	Test in fibrosis/cirrhosis models
Regulatory complexity	Multifunctional products are hard to classify	Delayed approval	Simplify design and define critical quality attributes
Cost	Complex formulations may be expensive	Limited global use	Develop affordable, scalable platforms
Endosomal escape	RNA delivery remains inefficient	Low potency	Improve ionizable lipids and responsive systems
Long-term accumulation	Nondegradable materials persist	Chronic toxicity risk	Prefer biodegradable materials

2. Future Perspectives

Future HCV nanomedicine should be more selective, disease-aware, and clinically realistic.[29,57-60]

1.

Disease-stage-specific nanoparticle design: Chronic hepatitis, fibrosis, compensated cirrhosis, and decompensated cirrhosis are not the same delivery environment. Nanoparticles should be optimized according to sinusoidal structure, macrophage activation, receptor expression, and extracellular matrix density.

2. Adjunctive use with DAAs: Nanoparticles should be developed as adjuncts for special populations, not as universal replacements for oral therapy.

3. Antiviral plus antifibrotic delivery: Post-SVR patients with advanced fibrosis need liver repair strategies. Co-delivery of antiviral and antifibrotic agents could be useful in patients treated late in disease progression.

4. Biomimetic carriers: Hepatocyte-membrane-coated particles, immune-cell-derived vesicles, or engineered exosomes may improve compatibility and cell-specific interaction.

5. Smart nanoparticles: ROS-responsive, enzyme-responsive, and pH-responsive systems could release cargo preferentially in inflamed or fibrotic liver tissue.

6. AI-assisted formulation design: Machine learning can help predict particle size, encapsulation, transfection efficiency, toxicity, and liver targeting. Recent work has explored machine-learning-guided LNP design for mRNA delivery, illustrating how computational screening may reduce experimental burden.

7. Organoids and liver-on-chip screening: These models can reduce translational failure by incorporating human liver architecture, flow, multicellularity, and disease states.

8. Transplant-related applications: Nanoparticles could be explored for preventing recurrence, modulating ischemia–reperfusion injury, or delivering local immunomodulators after liver transplantation.

9. Theranostic systems: Inorganic or hybrid nanoparticles may combine imaging, fibrosis staging, antiviral delivery, and response monitoring.

10. Affordable nanomedicine: Global HCV elimination requires scalable and cost-sensitive technologies. Complex personalized nanomedicines may be scientifically impressive but clinically irrelevant if they cannot be manufactured affordably.

3. Conclusion

Liver-targeted nanoparticle-based delivery systems remain scientifically relevant for hepatitis C therapy, but their role must be carefully defined. The success of DAAs has shifted the field away from broad antiviral replacement strategies and toward specialized delivery problems: nucleic acid therapeutics, resistant infection, advanced liver disease, post-SVR complications, and multifunctional liver repair.

Nanoparticles offer clear technical advantages, including hepatocyte targeting, protection of unstable cargo, improved solubility, controlled release, and combination delivery. Liposomes, lipid nanoparticles, polymeric nanoparticles, micelles, dendrimers, inorganic carriers, exosomes, and biomimetic systems each offer distinct opportunities. However, clinical translation remains limited by safety, cost, reproducibility, regulatory complexity, and the high benchmark established by oral DAAs.

Future research should move beyond formulation novelty alone. The next generation of HCV nanomedicine should be disease-stage-specific, scalable, safe in injured liver, compatible with existing antiviral regimens, and affordable enough for real-world use. The strongest future lies in precision hepatology: targeted systems that treat not only the virus, but also the damaged hepatic microenvironment left behind.

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