RESEARCH PAPER

Targeted PLGA Nanocarrier in Treatment of Liver Cirrhosis: A Comprehensive Review

Kazi Farzana I[1], Kale Monika H[1*], Patil Utkarsha B[1], Chopade Smital S[1], Khilari Madhavi M[1], Burli Sanganna[1*], V. R. Dhole[1], Prashant S. Kumbhar[1], Sachin S. Mali[2]

[1] Department of Pharmacology, Ashokrao Mane College of Pharmacy, Peth-Vadgaon, Kolhapur, Maharashtra, India.

[2] Department of Pharmaceutics, Bharati Vidyapeeth College of Pharmacy, Kolhapur, Maharashtra, India.

[*] Corresponding Author: Burli Sanganna, Department of Pharmacology, Ashokrao Mane College of Pharmacy, Peth-Vadgaon, Kolhapur, Maharashtra, India. Email: scburli@gmail.com

ABSTRACT

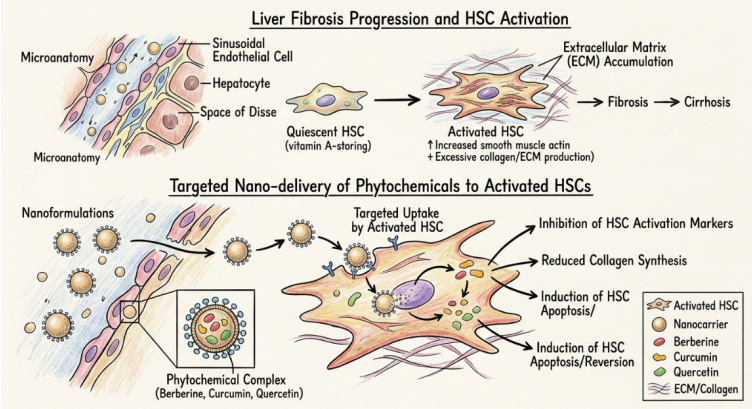
For the human body to function physiologically, the liver is an essential organ. The body's detoxification activities, red blood cell storage and breakdown, plasma protein, hormone synthesis and red blood cell destruction are all regulated by the liver; as a result, the liver is susceptible to their negative effects and an increased risk of disease. Hepatitis, liver fibrosis, cirrhosis, fatty liver, and diseases caused by drugs and alcohol are the most common side effects of long-term liver diseases. In hepatic fibrosis, stellate cells in the liver become activated, leading to the accumulation of cytosolic matrix proteins and the subsequent progressive damage to the liver. Globally, liver cirrhosis is becoming a bigger public health concern. A major cirrhosis consequence that is linked to worse outcomes is malnutrition. The prevalent metabolic disease known as metabolic syndrome has emerged as a global public health concern. Drugs that contain natural ingredients have gained popularity as supplements or substitutes for standard chemical therapies because of their easy accessibility and minimal adverse effects. These molecules may become more soluble, bioavailable, and perhaps more effective if they are nanosized. This study offers a thorough review of the use of Nanoformulation based on natural ingredients in management of metabolic syndrome. Numerous phytochemicals have been nanosized, such as berberine, curcumin, naringenin, Capsicum oleoresin, emodin, resveratrol, gymnemic acid, quercetin, baicalin, stevioside, scutellarin, silybin, and others. The pathological end consequence of some chronic liver illnesses is liver cirrhosis, and cirrhosis is proceeded by fibrosis. Liver fibrosis and cirrhosis are affected by a wide variety of cell types, cytokines, and microRNAs. Hepatic stellate cells (HSCs) must be activated in order for fibrosis to advance. Goal of this thorough review is to provide academics, physician and pharmaceutical industry experts insightful information on how targeted drug delivery is changing in the context of liver cirrhosis therapy.

Keywords: Liver, Hepatitis, Cirrhosis, Nanoformulation, cytokines, Sinusoidal endothelial cell

How to cite this article: Kazi Farzana I, Kale Monika H, Patil Utkarsha B, Chopade Smital S, Khilari Madhavi M, Burli Sanganna, Dhole V R, Kumbhar P S, Mali S S. Targeted PLGA Nanocarrier in Treatment of Liver Cirrhosis: A Comprehensive Review. Int J Drug Deliv Technol. 2026;16(37s): 915-925. DOI: 10.25258/ijddt.16.37s.117

Source of support: Nil.

Graphical Abstract:



1. INTRODUCTION

The liver is an excellent organ that performs many different functions; it is also the body's powerhouse [1]. The liver is a main hub for a wide variety of bodily processes. Some examples of these methods are breakdown of xenobiotic compounds (such as many modern pharmaceuticals), maintenance of healthy lipid and cholesterol levels, regulation of blood volume, support of immune system, and endocrine modulation of growth signalling pathways [2]. In Cirrhosis develops when the liver has scarred enough from a number of diseases and disorders, such as chronic alcoholism or hepatitis, to be noticeable. Liver performs a number of essential tasks, such as cleaning your blood, producing essential nutrients, and purifying your body of dangerous substances. When your liver is damaged, you develop cirrhosis. The liver constantly tries to repair itself if it becomes injured. The process causes scar tissue to form. The liver's capability to function is hampered by the increasing amount of scar tissue that accumulates as cirrhosis advances [3]. Above 160 million individuals international had cirrhosis in 2017, and over 0.8 million cirrhosis patients passed away each year [4,5]. Globally, cirrhosis is a major contributor to morbidity and mortality in individuals with chronic liver disease. Cirrhosis was linked to 2.4% of all fatalities worldwide in 2019.[6] Compared to other major chronic diseases, there is less public knowledge and concern about cirrhosis despite its global incidence and disease burden.When particles (>6 nm) are not removed by the kidney, the liver serves as a biological barrier and may absorb the great majority of given nanoparticles (NPs) from the bloodstream. However, NPs must overcome a number of biological obstacles in the liver to be successfully absorbed by the various liver cell populations [7]. Hepatocellular carcinoma (HCC), liver fibrosis, and viral hepatitis have all been successfully treated with albumin-based nanoparticles (NPs) for liver-specific targeting. For DOX, galactose-modified derivatives demonstrate better liver targeting and stability, whereas oridonin's galactosylated bovine serum albumin (BSA) exhibits less systemic toxicity [8]. Exactly seven with four original investigations, one meta-analysis, and two reviews, this special issue "The Clinical Management of Liver Cirrhosis: Current Concepts, Recent Advances and Future Trends" delves into a wide array of significant issues and cirrhosis-related repercussions. Two of them center on NITs, or non-invasive tests, that can be employed to assess fibrosis in the liver. Since NITs have become so commonplace in clinical practice, liver biopsies have become much less common; these days, they are more often used to diagnose individual cases of liver disease rather than to stage fibrosis [9]. The biggest study that has been done so far indicates. Cirrhosis is the fourth leading cause of mortality globally from non-communicable illnesses; over the past 20 years, the combined number of fatalities from cirrhosis and liver cancer has increased by over 50 million annually [10,11].

2. PATHOPHYSIOLOGY

The production of proteins such as clotting factors, albumin, detoxification, complement factors, and vitamin A storage all depend on the liver. It takes role in the breakdown of carbs and fats. Regardless of the underlying etiology, hepatitis and steatosis frequently accompany cirrhosis. Alterations are fully rescindable if reason is fixed at this point. Scar tissue growth in cirrhosis substitute’s healthy parenchyma, obstructs blood flow to the organ, and impairs normal function. Studies reveal that stellate cell, which typically accumulates vitamin A, plays a vital part in development of cirrhosis. Injury to the hepatic parenchyma brought on by inflammation activates stellate cells, promotes fibrosis, and impedes blood flow. The entire liver architecture is replaced with hepatocyte nodules that are separated by fibrous tissue bands. Chronic liver damage causes inflammation, necrosis, and eventually fibrosis [12].

Hyperdynamic circulation and portal hypertension are leading causes of death and disability in cirrhotic patients. The formation of collateral circulation and hyperdynamic circulation are outcomes of portal hypertension, which is caused by intrahepatic fibrosis and changes in Vaso regulation. One of the functions of SECs is to secrete endothelin-1 (ET-1) and nitric oxide (NO) into the liver. These chemicals regulate blood flow to the sinusoids by acting on HSCs to constrict sinusoids. Cirrhosis patients have rise in ET-1 synthesis and a decrease in NO production, both of which cause a sensitivity increase in ET-1 receptors. The consequence is an increase in intrahepatic vasoconstriction and resistance (Figure 1), which in turn causes portal hypertension [13].

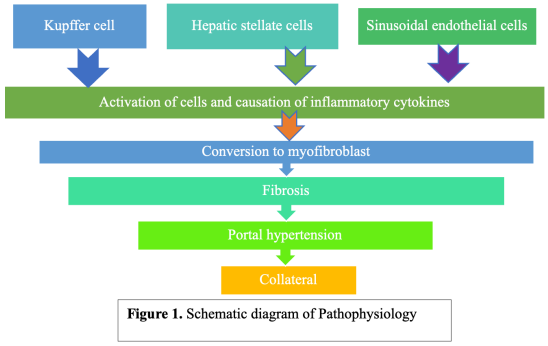


Figure 1. Schematic diagram of Pathophysiology

Table 1: Etiology

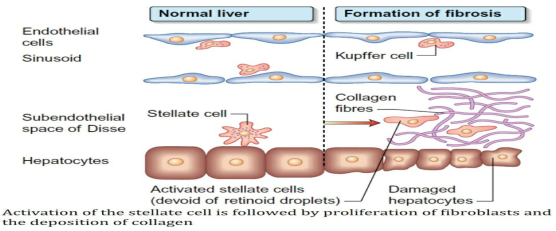
Autoimmune		Autoimmune hepatitis	
Viral infectious	**Metabolic**	**Cholesteric**	**Vascular**
Hepatitis B	Alcohol	Primary biliary cirrhosis	Right heart failure
Hepatitis C	Toxins, medications	Primary sclerosing cholangitis	Budd–Chiari syndrome
Schistosomiasis	Hereditary hemochromatosis	Biliary atresia	Alpha-1-antitrypsin deficiency
	Wilson's disease	Secondary biliary cirrhosis	Sarcoidosis
	Non-alcoholic steatohepatitis		Cystic fibrosis
	Insulin resistance		

Chronic (long-term) liver disorders that harm liver tissue are what create cirrhosis. Cirrhosis may not develop for several years after liver damage. In the US, chronic alcoholism is one of key causes of cirrhosis. Overindulgence in drinking can lead to liver enlargement and cirrhosis over time. Each person is affected differently by the amount of alcohol that causes cirrhosis. Another collective cause of cirrhosis is chronic hepatitis C. Hepatitis C causes the liver to enlarge, which might eventually result in cirrhosis. Cirrhosis develops in around one in four individuals by chronic hepatitis It can also result from chronic hepatitis B and hepatitis D. Flow of bile to
small intestine is restricted or stopped by bile duct disease. The liver swells and may develop cirrhosis when the bile backs up in the liver. Primary sclerosing cholangitis and primary biliary cirrhosis are two prevalent bile duct disorders. Cirrhosis can result from some hereditary illnesses, as shown in Table 1. [14].

4. PATHOGENESIS Initiation of fibrosis is associated with activated platelets, stellate cells, Kupffer cells, and damaged hepatocytes. Stem cells are stimulated by a variety of signals, including reactive oxygen intermediates, autocrine and paracrine signals, and various cytokines and their receptors. During the initial stages of activation, the retinoids are lost by the expanded stellate cells because the receptors for proliferative and fibrogenic cytokines, like PDGF**2)** and TGF-β1, an extremely powerful fibrogenic mediator, are upregulated. The release of cytokines by inflammatory cells causes fibrosis. In the Disse region, fibronectin and collagen types I and III take the place of the usual matrix.
Subendothelial fibrosis causes endothelial function loss and liver function impairment. Liver fibrosis is associated with improved levels of tissue inhibitors of metalloproteinases, which block the breakdown of collagen by matrix metalloproteinases. Liver fibrosis can be reversible in its early stages when inflammation

3. ETIOLOGY [14]

is reduced by blocking or eliminating viruses. Cirrhosis is characterized pathologically by regeneration of nodules disconnected via fibrous septa and a decrease in blood flow throughout the liver due to the loss of normal lobular architecture inside nodules. Congestion within the spleen leads to hypersplenism and an increase in platelet sequestration. Illustrated in figure 2 [14].



Activation of the stellate cell is followed by proliferation of fibroblasts and the deposition of collagen

Several Cell Types

1) Hepatic stellate cells (HSCs) The normal liver's Disse region is home to HSCs, which have several original names such as fat-storing cells, Ito cells, lipocytes, perisinusoidal cells, or vitamin A-rich cells. Keeping retinoids and vitamin A in reserve is their principal function. Fibrosis of the liver develops as a consequence of the actions of activated HSCs, which include migration and proliferation, contraction upon differentiation into myofibroblasts, and an abundance of collagen and other ECM [15].

Kupffer cells (KCs) KCs, sometimes referred to as stellate macrophages or Borowicz-Kupffer cells, are specialized macrophages found in the reticuloendothelial system (RES), which includes the lining walls of the liver's sinusoids. Research using animal models has demonstrated that KCs have a role in the etiology of a number of liver disorders. Numerous harmful variables, including iron deposition, alcohol, high-fat diets, and viral infections, can activate KCs. Activated KCs function as antigen-presenting cells during viral infection and kill

hepatocytes by generating toxic soluble mediators [16].

3) **Hepatocytes** Hepatocyte apoptosis occurs often in liver injury and plays a role in tissue inflammation, fibrogenesis, and cirrhosis formation [17]. The steatohepatitis increases the degree of the disease and active nuclear factor (NF)-κB are correlated with Fast-mediated hepatocyte apoptosis Both ethanol consumption and HCV infection cause hepatocyte apoptosis in humans and animal models; this initiation may be linked to Bcl-2 signalling downregulation [18].

4) **Liver sinusoidal endothelial cells (LSECs)** The sinusoidal wall, sometimes denoted to as endothelium or endothelial lining, is made up of LSECs. Fenestrae on endothelium's surface are structural feature of LSECs. Hepatic dysfunction in liver cirrhosis is thought to be largely caused by defenestration and capillarization of LSECs, which limit substrate altercation [19].

5. HERBAL PLANTS USED IN LIVER CIRROHSIS

Table 2. Herbal plant used in liver protective

Herbal plant	Family	Chemical constituent	Uses	Re
Acacia Catechu	Leguminosae (Fabaceae)	• Catechins • Catechutanic acid • Quercetin • **Cyanidanol (+)**	▪ Astringent ▪ Digestive ▪ Antipyretic ▪ Antidiarrheal ▪ **Liver disease**	
Andrographis Paniculata	Acanthaceae	• Diterpenes • Lactones • Flavonoids • Alkenes • Ketones Aldehydes	▪ Antioxidant ▪ Anti-inflammatory ▪ Antimicrobial ▪ Antiviral ▪ Antitumor	
Astercantha longifolia	Acantheacea	• ß-sitosterol • Lupeol • Flavonoids • Terpenoids • Steroids	▪ Antipyretic ▪ Hepatoprotective ▪ Jaundice ▪ Hepatic obstruction ▪ Rheumatism ▪ Inflammation ▪ Pain	
Allium Sativum	Alliaceae	• Allicin • Diallyl sulphide • Diallyl trisulphide • S-aalylmercaptocysteine	▪ Antibacterial ▪ Antiviral ▪ Antifungal ▪ Antiprotozoal ▪ Antiparasitic ▪ Liver protective ▪ Anti-cancer	
Azadiractha ndica	Meliaceae	• Isozadirolide • Nimbaflavone • Nimbolide • Quercetin • Rutin • Vilasanin	▪ Antiviral ▪ Antifungal ▪ Antibacterial ▪ Antimalarial ▪ Hepatoprotective ▪ Immunostimulant	
Berberis aristata	Berberidaceae	• Bisisoquinoline • Protoberberine	▪ Hepatoprotective ▪ Antidiabetic ▪ Anticancer ▪ Antimalarial ▪ Anti-inflammatory ▪ Antioxidant	

6. NANOFORMULATION

Targeted nano-drug delivery systems, nano-targeted preparations, or specific drug carriers are a kind of drug delivery technology that concentrates a drug on a specific organ or tissue. Its characteristics include a wide drug loading range, minimum adverse effects, and long duration of therapeutic activity, targeting, and specificity. In comparison to more traditional formulations, it has a number of benefits, including enhanced solubility of hydrophobic medicines, increased stability in vivo, and enhanced epithelial permeability [35]. The ability of targeted preparations to deliver medications to the intended spot is their most notable feature when compared to standard preparations. Drugs' bioavailability and therapeutic impact can be enhanced to the greatest possible degree. An increasing number of cancer treatments are utilizing tailored preparations of nanoparticles, liposomes, polymer micelles, dendrimers, and microspheres, thanks to the advancements in nanotechnology. It has been thoroughly studied and given a lot of attentions shown below in figure 4 [36].

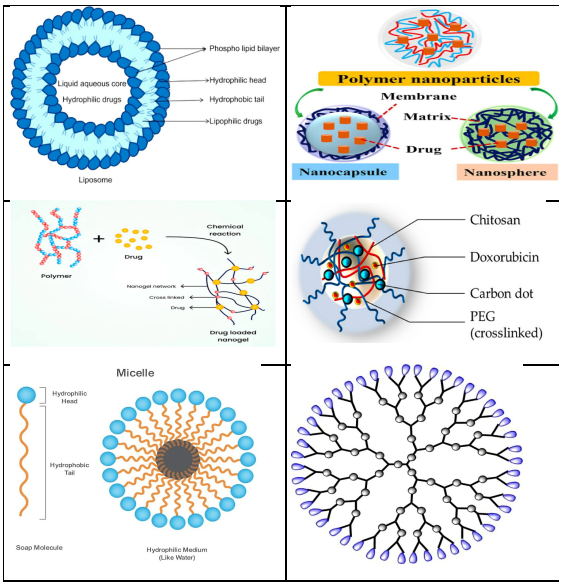


Figure 4: Types of Nanoformulation

6.1 Liposomes Its distinct phospholipid bilayer structure, which is comparable to that of a natural membrane, has improved its compatibility with the BBB's lipoidal layer and facilitated medication entry into the brain. Such surface modification of liposomes to improve the drug's bioavailability in the brain area [37].

6.2 Polymeric Nanoparticle By offering better protection and enabling drug distribution at particular locations of action, nanoparticles have probable to significantly increase the therapeutic efficiency of medications. Polymeric, inorganic, and lipid-based nanoparticles are among the many varieties of nanoparticles that have demonstrated potential for drug delivery uses [38]. In order to be effective, polymeric nanoparticles need to be able to go across a variety of biological obstacles in extracellular and intracellular settings. These obstacles are frequently unique to a certain medication, delivery method, illness, or endogenous target. Low molecular weight drug delivery is characterized by issues such as solubility, toxicity, and controlled release; in contrast, the delivery of larger therapeutics such as nucleic acids or proteins usually necessitates enhanced stability and targeted release at specific cell regions [39].

6.3 Dendrimers Dendrimers are three-dimensional spherical polymers that are monodisperse and highly branched. Various synthetic procedures can regulate their structure, including their size, shape, charge, and solubility properties. Three materials are frequently used in delivery systems: polypropylenimine, poly(L-lysine) dendron, and PAMAM. Dendrimers are readily surface-modifiable and can be coupled to genes or medications. The biomedical fields have made extensive use of them [40].

6.4 Magnetic Nanoparticle Under the influence of an external magnetic field, magnetic nanoparticles laden with medication are delivered to the tumour site using a magnetic drug delivery system. However, the creation of this delivery method requires that the nanoparticles only show magnetic actions when open to an external magnetic field, and that they become inactive when external magnetic field is withdrawn. Fortunately, because of the existence of a single domain state, very small nanoparticles with sizes under 10 nm typically acquire such magnetic characteristics. On the other hand, the multidomain structure of massive magnetic particles is widely understood. Domain barriers divide these multidomain situations [41].

6.5 Polymeric Micelle Micelles are particulate self-assemblies in water that are formed by a single strand of hydrophilic and hydrophobic "blocks" (AB-type) on a linear amphiphilic macromolecule (each copolymer strand is amphiphilic). The particles are far smaller than phospholipid carriers, with diameters ranging from 10 to 100 nm [42,43]. Highly controlled block copolymers with a unique core-shell structure make up polymeric micelles. Drugs can be introduced into the micelle core via functional groups like amines and carboxylic acids in the core-forming regions [44].

6.6 Nanogel Biodegradable nanoparticles with a rh of up to 1 μm and supramolecular dendrimers with a rh of less than 10 nm are among the many known physical

nanocarriers that have been utilized as DDS; it is only recently that nanogels have been added to this vast array. "Nanogels" are the tiny hydrogel particles made from mechanically or chemically crosslinked polymer networks. When dispersed in water, swollen nanogel networks may hold a lot of water since they are soft. Biological substances and pharmaceuticals can be loaded into nanogels to create hydrophilic particles with excellent dispersion stability through an involuntary process involving interactions between the drug and the polymer matrix. Preclinical research on nanogels has shown that they may physically protect biological molecules against degradation in vivo; this includes everything from small pharmaceuticals to biomacromolecules. After the first decade of research, nanogels demonstrated significant potential for triggered drug-release applications, multifunctional nanocarrier synthesis (e.g., theranostics), and systemic drug delivery [45].

Table 3: Natural hydrophilic polymer

Natural Hydrophilic Polymers	
Proteins	**Polysaccharides**
Albumin	Dextran
Gelatin	Alginates
Legumin	Agarose
Lectins	Chitosan

Table 4: Synthetic hydrophobic polymer

Synthetic Hydrophobic Polymers	
Pre-polymerized	**Polymerized in process**
Polystyrene	PMMA
Poly lactic acid (PLA)	PBCA
Poly (E-Carolactone) (PECL)	Poly (Isobutylcyano acrylates) (PICA)
Poly lactic co glycolide (PLGA)	PHCA

7. CLASSIFICATION OF NANO-PARTICLES

Particulate dispersions or solid particles between 10 and 1000 nm in size are referred to as nanoparticles. A variety of methods are used to encapsulate, dissolve, trap, or attach the drug to a nanoparticle matrix. Various preparation techniques allow for the production of nanoparticles, nanospheres, or nano capsules. Whereas nanospheres use a matrix system to physically and uniformly disperse the drug, nano capsules use a hollow encased by a unique polymer membrane to hold the drug. (Tables 3 and 4) as demonstrated in reference [46].

- Natural polymers
- Synthetic polymer
- Semi – synthetic polymer

7.1 METHODS FOR NANOPARTICLE PREPRATION Optimal methods for generating nanoparticles are determined by the drug to be loaded and the physicochemical properties of the polymer. [47] Nanoparticles have found widespread usage in many dosages forms due to their excellent solubility, small size, and exceptional penetrability. Nanoparticles can be prepared using a variety of methods. Some of these include the following: the Salting Out Method, the Solvent Displacement/Precipitation Method, the Polymerization Method, the Coacervation or Ionic Gelation Method, the Double Emulsion and Evaporation Method, the Salting Out Method, the Emulsions Diffusion Method, and many more. Vaccination, gene transfer, cell-specific internalization, and microwiring are some of the many applications of nanoparticles. In the medical field, nanoparticles are also utilized in orthopaedic implants and cancer treatment. These days, nanoparticles are utilized in nearly every formulation because to their great solubility and quick penetration [48].

A. From dispersion of performed polymer

- ✓ Solvent evaporation
- ✓ Emulsification
- ✓ Dialysis
- ✓ Nanoprecipitation
- ✓ Supercritical fluid technology
- ✓ Salting out

B. From polymerization of monomer

- ✓ Mini emulsion
- ✓ Emulsion
- ✓ Microemulsion
- ✓ Interfacial polymerization

1) **Solvent evaporation** This technique uses high-speed homogenization or ultrasonication to create emulsions after dissolving polymers in volatile liquids. Once single or double emulsions are made, the volatile solvent is evaporated. Ultracentrifugation is used to gather these nanoparticles, and lyophilization is used to create a dry product [49].

2) **Nanoprecipitation** The solvent displacement method is another name for the nanoprecipitation technique. Interfacial deposition of the polymer takes occurred when a polymer displaces by a semipolar solvent that is miscible by water Nanodroplets are created when solvent quickly diffuses into nonsolvent phase, increasing surface area [50].

3) **Emulsification** After dissolving in a solvent that is only weakly soluble in water, the polymer becomes completely soaked with the liquid. In an aqueous solution, it is subsequently emulsified. Nanoparticles are created when the solvent diffuses to the exterior phase [51].

4) **Salting out** Beginning with a water-miscible solvent in an aqueous solution, the salting-out method separates the two. The sodium-out agents and colloidal stabilizers are added to an aqueous gel that is made by emulsifying the polymer and active ingredient in a solvent. The polymer dissolved in the emulsion droplets precipitates out when the emulsion is diluted with a considerable excess of water, creating an effect similar to a reverse salting-out [52].

5) **Dialysis** After dissolving the polymer in an organic solvent, it is dialyzed using a dialysis tube that has a suitable molecular-weight cutoff in opposition to a solvent that is immiscible with it. The polymer clumps together as the solvent within the membrane is transferred, resulting in the formation of uniform nanoparticles [53].

6) **Super critical fluid technology** Dense gas technology and supercritical fluid are substitutes for organic solvents in the creation of nanoparticles that are safer for the environment [54].

7) **Emulsion** Nanoparticles are frequently created by the emulsion polymerization process. The ingredients include a surfactant, water, an initiator that dissolves in water, and a monomer that has limited solubility in water. When an initiator molecule an ion or a free radical colides with a monomer molecule in the continuous phase, the result is a nanoparticle [55].

8) **Mini emulsion** Water, monomer combination, co-stabilizer, surfactant, and initiator make up a mini emulsion polymerization. The mini emulsion polymerization process uses a high-shear device (ultrasound, etc.) and a low-molecular-mass chemical as the co-stabilizer [56].

9) **Microemulsion** Emulsion polymerization and microemulsion polymerization have different kinetics. When using microemulsion polymerization, particle size is considerable smaller [57].

10) **Interfacial polymerization** A polymerization process takes place at the interface of the two liquid phases that include two reactive monomers or agents: the continuous phase and the dispersed phase [58].

8. CONCLUSION

Current treatment approaches continue to be challenged by the complexity of liver cirrhosis, which is caused by oxidative stress, inflammation, increasing fibrosis, and ongoing hepatic damage. The majority of traditional medications are constrained by low absorption, quick clearance, and insufficient targeting of diseased liver compartments, despite the variety of therapy options available. The creation of more potent and focused treatments is therefore still a top research objective.

Because of their controlled release behaviour, biodegradability, biocompatibility, and capacity to shield encapsulated chemicals from premature breakdown, PLGA nanoparticles have become a viable therapeutic agent delivery technology. Research results show that PLGA-based Nanoformulation can improve therapeutic efficacy and greatly increase drug accumulation in the liver, especially when utilised to deliver natural bioactive compounds with hepatoprotective and antifibrotic potential. Targeted distribution to hepatic stellate cells and other important fibrosis mediators is made possible by surface modification of PLGA nanoparticles, which also improves pharmacological performance and minimises off-target effects.

PLGA Nanoformulation loaded with herbal or synthetic medicines may be more effective than their free drug counterparts at reducing fibrosis, modifying inflammatory pathways, and improving liver architecture, according to data from current in-vitro and in-vivo research. Despite their promise, these developments still need thorough clinical testing to determine dosage safety, long-term effectiveness, scalability, and regulatory viability.

In conclusion, incorporating PLGA nanotechnology into management of liver cirrhosis is an innovative therapeutic method that has great promise for overcoming contemporary therapy constraints. To turn these experimental results into useful medicinal applications, pharmacology, nanotechnology, and clinical research must continue their joint efforts. This approach has potential for future therapeutic development and may lead to safer, more focused, and more successful treatments for liver cirrhosis.

Declarations

Ethical Approval and Consent to Participate

Not applicable. This study did not involve human participants or animals.

Consent for Publication

Not applicable.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article. Additional data may be obtained from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Funding

The authors received no specific funding for this work.

Authors' Contributions

All authors contributed equally to the conception, design, experimental work, data analysis, and manuscript preparation. All authors have read and approved the final manuscript.

Acknowledgements

The authors express their sincere gratitude to all the respective institutions for providing necessary facilities, support, and encouragement to carry out this research work.

9. REFRENCE

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