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Review Article

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Liver Targeting Novel Trends In Therapies

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Abstract

Background: *In this review Novel strategies for site-specific delivery of active pharmaceutical ingredients to different types of liver cells like Hepatic stellate cells [HSCs], active Kupffer cells, sinusoidal endothelial cells etc. have been discussed. The most prevalent liver ailments are hepatitis, alcoholic or non-alcoholic liver disease, hepatocellular carcinoma, hepatic venous-occlusive disease, liver fibrosis, and cirrhosis.*

Method: *Literature was searched through various online resources for the recent advances in liver-targeted site-specific delivery using various approaches. We focused on the use of novel targeted delivery to improve Drug efficacy, dose reduction and Rapid onset of action.*

Results: *Novel medicines aim to minimize unfavorable side effects by either sustaining drug action at a set rate or delivering the drug at a suitable time in the body. Therapeutic nanocarriers and their surface modification with particular ligands including carbohydrates, peptides, proteins, and antibodies are two main strategies that have been suggested to optimize the transport of various medications to the liver and hepatocytes. It subsequently lowers the toxicity and prolongs the drug's time in the systemic circulation.*

Conclusion: *The current review provides information on various liver illnesses as well as the targeting techniques used to concern hepatic anatomy and disease etiologies.*

Keywords: Liver Cells, Liver Disease, Liver drug Targeting, Nanocarriers, Ligand mediated delivery

Introduction

Drug delivery refers to methods, formulations, technologies, and systems for conveying a pharmaceutical substance in the body as needed to accomplish the intended therapeutic effect safely. The novel drug delivery system is the most appropriate and approachable in developing the delivery system that improves the therapeutic efficacy of both new and pre-existing drugs, thus providing controlled and sustained drug delivery to the specific site and meeting the real and appropriate drug demand of the patient [1-2]. As we are aware the liver is the body's largest organ, accounting for 1.5–2.5% of lean body mass and weighing 1–1.5 kg. The liver's size and shape might vary, but they typically correspond to a long, lean, or square-shaped body. Located below the right lower rib cage and at the diaphragm, this organ is located in the upper right quadrant of the abdomen and extends to varying degrees into the upper left quadrant [3]. The majority of cells in the liver are hepatocytes, which account for two-thirds of the liver's mass. Kupffer cells [reticuloendothelial system members], stellate [Ito or fat storing] cells, endothelial cells and blood vessels, bile ductular cells, and supporting structures are the remaining cell types [4]. Liver disorders, in particular Hepatitis, alcoholic or non-alcoholic liver disease, hepatocellular carcinoma [HCC], hepatic venous-occlusive disease, liver fibrosis, and cirrhosis are a few of the leading causes of disability and mortality worldwide. Due to the scarcity of curative therapy options other than liver resection and transplantation, such liver disorders continue to be a major public health concern worldwide. These demand long-term pharmaceutical therapy. Liver-specific medicine administration lowers negative effects by limiting drug distribution in non-target organs while increasing therapeutic efficacy by increasing drug concentration in target cells. It achieves target drug action by delivering the drug to a specific target cell type via carriers or chemical derivatization, localising drug action by spatially situating controlled release systems nearby, inside the sick tissue or organ, or localising drug action utilising controlled release systems [5-7]. The current study provides information on various liver illnesses as well as the

targeting techniques used concerning hepatic anatomy and disease etiologies.

Drug targeting strategies

The answer to all of these issues lies in drug targeting. A very broad definition of drug targeting is the drug's capacity to accumulate in the target organ or tissue in a selective and significant manner, independent of the place and modes of its delivery. Under such circumstances, the drug's local concentration at the illness site[s] should ideally be high, but that of the drug in other organs and tissues that are not the goal of the treatment should ideally be below a predetermined minimum level to prevent any adverse side effects. Drug targeting has the following benefits: The expense of therapy as well as the complexity of drug administration procedures may be considerably decreased. Drug concentration in the needed sites may also be sharply enhanced without adverse effects on non-target compartments [8].

Currently being researched in various experimental and clinical contexts are the following primary medication targeting schemes:
i. Applying the medication directly to the organ or afflicted tissue;
ii. Through leaky vasculature [tumours, infarcts, inflammation], the medication passively accumulates;
iii. Physical targeting of conditions like tumours or inflammation based on aberrant pH and/or temperature in the target zone [pH and temperature-sensitive medication carriers];
iv. The use of an external magnetic field to target pharmaceuticals magnetically linked to paramagnetic carriers;
v. Utilizing molecules as vectors that have a strong affinity for the afflicted area.

Targeting the liver through a carrier-mediated approach nanoparticles

A nanoparticle is a microscopic particle with a dimension between 1 and 100 nanometers. The physical and chemical characteristics of nanoparticles, which are invisible to human sight, might differ dramatically from those of their bigger material counterparts. Magnetic nanoparticles targeting the liver have been used as contrast agents for magnetic resonance imaging [MRI] by lowering the relaxation time of protons in absorbing tissues to induce contrast effects under external magnetic fields [9-10]. Nanoparticles that degrade naturally are efficient medication delivery systems. Various polymers have been employed in drug delivery research because they can deliver drugs to target sites efficiently, increasing therapeutic benefits while reducing side effects [11].

Nanoparticles have helpful Control release qualities and aid in improving the stability of medicines and proteins. Typically, nanoparticles range in size from 10 to 1000 nm. Drugs are dissolved, trapped, encapsulated, or connected to a nanoparticle matrix in nanoparticles. Depending on the preparation process, nanoparticles, nanospheres, or nanocapsules can be produced. Various ligands, including folic acid, asialoglycoproteins, galactosyl residues, and glycyrrhizin derivatives, have been added to drug carriers to target polymeric nanoparticles in the liver. Hepatocellular carcinoma [HCC] is a major contributor to the rising mortality rate in the elderly haemophilia population [12]. Complex epigenetic changes and mutations that activate molecular signalling pathways linked to cellular replication and the avoidance of apoptosis play a role in the multi-step process of chronic liver disorders progressing to HCC [13,14]. The standard systemic chemotherapeutic drugs available for HCC are doxorubicin, cisplatin, 5-fluorouracil, and sorafenib, either alone or in combination [15-17].

Various studies have demonstrated that targeted drug delivery can improve drug efficiency. Various ligands, including folic acid, asialoglycoproteins, galactosyl residues, and glycyrrhizin derivatives, have been added to drug carriers to target polymeric nanoparticles in the liver. C. Li et al colleagues created albumin nanoparticles containing galactose residues on the exterior to successfully target the delivery of Oridonin into liver cancer cells [18]. As a targeted drug delivery system for the treatment of liver cancer, Liang et al. prepared Paclitaxel-loaded poly [-glutamic acid]-poly [lactide] nanoparticles. They then studied the distribution of the particle size, the zeta potential, the drug-loading content and the drug-loading effectiveness of the prepared nanoparticles, as well as their release profile and cytotoxicity on HepG2 cells [a liver cancer cell line] [19]. Furthermore, the biodistributions of the produced nanoparticles in normal mice and hepatoma-tumour-bearing nude mice were examined in vivo. Norcantharidin-associated galactosylated chitosan nanoparticles were created by Q. Wang et al. for hepatocyte-targeted administration and their targeting properties were confirmed [20].

Mitoxantrone-loaded poly butyl cyanoacrylate [PBCA] nanoparticles are another polymeric nanoparticle in clinical trials. The radioactivity was found to be higher in the liver than in other organs and to be even higher in liver tumours than in normal liver tissue in mice after intravenous injection of H-mitoxantrone-PBCA. Patients with unresected hepatocellular carcinoma in the mitoxantrone-loaded PBCA nanoparticles group in phase II clinical study had median survival. Duration of 5.46 months, compared to 3.23 months in the mitoxantrone-free group. Note that anaemia and leucopenia were the two main harmful outcomes [21]. Ping et al. attached glycyrrhizin [GL] to chitosan nanoparticles [CS-Nanoparticles], which were created by an ionic gelation procedure. These nanoparticles were created for a drug delivery system that specifically targets the liver by glycyrrhizin's interaction with hepatocytes. The cellular absorption of glycyrrhizin chitosan nanoparticles was dependent on incubation duration and dose of nanoparticles, indicating that the internalization of these nanoparticles into hepatocytes was primarily mediated by a ligand-receptor interaction [22].

Liposomes

The terms "Lipos" [which means fat] and "Soma," which means body, are the origins of the phrase "liposome." For the delivery of nutrients and drugs, liposomes are bi-layer structures made of cho-

lesterol and phospholipids. One or more concentric lipid bilayers make up liposomes, which also have an internal aqueous volume [s]. Liposomes are typically unilamellar and have a diameter of 50 to 150 nm for drug delivery applications. Larger liposomes are quickly eliminated from the bloodstream. They have lipid bilayer architectures, which are made of lipid molecules in such a way that both hydrophilic and lipophilic medicines can be successfully captured in an aqueous volume completely encompassed by a membrane [23]. For instance, it has been demonstrated that cytostatic drugs like Adriamycin that target tumours are linked to Kupffer cell function loss, which contributes to the immunosuppressed state of patients. Surprisingly little has been done to use the high Kupffer cell uptake in drug-targeting strategies to treat liver disorders [24]. Introducing cells that recognise ligands on the liposomal surface makes it possible to selectively target the liposome for hepatocytes. Hepatocytes have a galactose receptor that detects the galactosyl residues in desolated serum glycoproteins. To target hepatocytes with liposomes, a galactose-terminated molecule, such as asialofetuin lactosylceramide, has been employed as the ligand [25]. Galactosylated liposomes were created by M. Hashida and his colleagues to target hepatocytes and to better understand how these liposomes travel. To target hepatocytes, the glycyrrhizin derivative is also employed as the ligand on liposomes [Table -2]

Table 2: Experimental details regarding Liposomes Targeting Liver cells

Sr no	TITLE OF RESEARCH	API ENCAPSULATED	TARGETING STRATEGIES	REFERENCES
1	Uptake of liposomes surface-modified with glycyrrhizin by primary cultured rat hepatocytes	30-stearyl glycyrrhizin	Targeting Rat hepatocytes with small unilamellar liposomes that contain 30-stearyl glycyrrhizin	25
2	Controlled biodistribution of galactosylated liposomes and incorporated probucol in hepatocytes-selective drug targeting	Probucol	To investigate the biodistribution of liposomal carriers and the inserted drug, galactosylated liposomes with cholesten-5-yloxy-N-(4-((1-imino-2-beta-D-thio-galactosyle thyl) amino) butyl) formamide (Gal-C4-Chol) as a homing device were created.	26
4	Liver-targeted gene transfer into a human hepatoblastoma cell line and in vivo by sterylglucoside-containing cationic liposomes	Sit-G-liposome/DNA complex	transfection efficiency of beta-sitosterol beta-D-glucoside (Sit-G)-containing liposome/DNA complex was developed to improve gene Transfection into a human hepatoblastoma cell line	27
5	Liposomal Oxymatrine in Hepatic Fibrosis Treatment: Formulation, In Vitro and In Vivo Assessment	Oxymatrine	Liposomes of oxymatrine conjugating d-alpha tocopheryl polyethene glycol 1000 succinate (OMT-LIP) were developed to enhance therapeutics of hepatic fibrosis	28

Noisome

Niosomes are a novel drug delivery technology that encapsulates the medication in a vesicle. Niosomes get their name from the fact that the vesicle is made up of a bilayer of non-ionic surface-active substances. The niosomes are minuscule in size and incredibly tiny. Niosomes, also known as non-ionic surfactant vesicles, are microscopic lamellar structures in aqueous fluids that range in size from 10 to 1000 nm and are made up of polyhedral, unilamellar, and multilamellar vesicles. They are on the nanometer scale in size. Niosomes, also known as non-ionic surfactant vesicles, are microscopic lamellar structures in aqueous fluids that range in size from 10 to 1000 nm and are made up of spherical, unilamellar or multilamellar and polyhedral vesicles. These also consist of inverse structures that only occur in non-aqueous fluids and are created by the subsequent hydration and self-assembly of non-ionic surfactant and cholesterol [29]. As is well known, Hepatitis C is a virus that infects the liver and, in extreme cases, results in liver damage and liver inflammation. Bloodborne pathogens can spread the hepatitis C virus [HCV]. HCV is typically disseminated by transfusions, poorly cleaned medical equipment, needlestick injuries in the healthcare industry, and blood-to-blood contact linked with drug injection usage. NHS-approved hepatitis C Convectional medicines include: Sofosbuvir, Combination of ledipasvir and sofosbuvir, Combination of ombitasvir, paritaprevir and ritonavir, taken with or without dasabuvir, Combination of elbasvir and grazoprevir, Combination of sofosbuvir, velpatasvir and voxilaprevir,

Combination of glecaprevir and pibrentasvir and ribavirin [30].

Novel targeted delivery such as Hashim, Fahima, and colleagues created Ribavirin niosomes utilizing the thin film hydration process and evaluated the effect of niosomal encapsulation on drug liver targeting in rats. The results demonstrate that the ribavirin liver concentration was substantially higher in the niosomal formulation than in the ribavirin-free solution. According to the findings, using niosomes as a drug delivery vehicle for ribavirin has strong liver targeting capabilities, which is likely to improve the efficiency of low doses of ribavirin while minimizing toxic side effects at higher dosages [31]. Hu, Xixi, and colleagues created galactose-modified pH-sensitive niosomes loaded with tanshinone IIA that can target hepatocellular carcinoma and rapidly release drugs within tumour cells. Pharmacokinetic investigations demonstrated that the vesicle system could greatly increase tanshinone IIA blood circulation time, and a bigger area under the curve indicated that the preparation had a stronger Pharmacological effect. Thus, the findings of biodistribution tests validated this preparation's capacity to target the liver in vivo. This type of niosome is intended to be a safe and effective drug delivery mechanism for liver cancer therapy [32].

Phytotomies

"Phyto" means "plant," and "some" indicates "cell-like." The active components of the standardized plant extract or its constituents are attached to phospholipids, primarily phosphatidylcholine, to form a lipid-compatible molecular complex. Phytosomes have better pharmacokinetic and pharmacological properties, and as a result, they can be utilized to treat acute and chronic liver illnesses of toxic, infectious, or degenerative origin. It can also be used to treat inflammation and in pharmaceutical and cosmetic formulations [33]. Phytosomes are created by reacting an aprotic solvent, such as methylene chloride, dioxane, or ethyl acetate, with phospholipids, such as phosphatidylcholine, phosphatidylethanolamine, or phosphatidylserine, which is also dissolved in the same solvent. After the complex compounds have been solubilized, they are isolated by removing the solvent under vacuum, freeze drying, or precipitation with non-solvents such as n-hexane [34]. Tung, B.T., Hai, N.T. and Son, P.K produced a phytosome curcumin formulation and tested its hepatoprotective efficacy on paracetamol-induced liver injury in mice the results demonstrated that Phytosomes have a greater hepatoprotective impact than curcumin-free curcumin. The administration of phytosome curcumin successfully inhibited paracetamol-induced liver injury in mice liver tissue, as demonstrated by a decrease in lipid peroxidation and increased enzymatic antioxidant activity of superoxide dismutase, catalase, and glutathione peroxidase. As a result, the study reveals that phytosome curcumin has high antioxidant activity and may have hepatoprotective properties [35]. According to Ravarotto et al, silymarin Phytosomes have higher anti-hepatotoxic action than silymarin alone and can protect broiler chicks from the toxic effects of aflatoxin B1 [36].

Ethosomes

Ethosomes have also been produced for the delivery of medications with poor skin penetration. Ethosomes are soft lipid vesicles with sizes ranging from tens of nanometers to microns that contain phospholipids, relatively high concentrations of alcohol [ethanol and isopropyl alcohol], and water. Ethanol functions as a penetration enhancer, fluidizing the ethosomal lipids and stratum corneum bilayer, allowing soft, flexible vesicles to pass through the disordered lipid bilayer. The high ethanol concentration [20-50%] is the primary reason for the improved skin penetration ability. Ethanol gives Ethosomes a surface negative net charge, which reduces the size of vesicles. As a result, as ethanol concentration decreases, the size of ethosomal vesicles increases. Elsayed, Mahmoud, and colleagues used the cold approach to create LUT [Luteolin] loaded ethosomal nanoparticles [LUT-ENPs]. The selected formulation factors were analyzed and optimized using a full factorial design and response surface approach. The LUT-ENPs were semi-spherical in shape and had high entrapment efficiency. After treatment with LUT-ENPs, Histopathological investigation revealed a modest number of hepatic adenomas and a considerable decrease in neoplastic hepatic lesions [37].

Emulsomes

Emulsome is a lipid-based drug delivery device that is primarily intended for the parenteral administration of medicines with low aqueous solubility. Nanosize Lipid particles [bio adhesives nanoemulsion] were minute lipid assemblies in emulsomes with a polar centre. The internal core is composed of fats and triglycerides that are stabilized as an o/w emulsion by the addition of a high concentration of lecithin. Emulsomes combine the properties of liposomes with emulsions. Because the solidified or semi-solidified interior oily core provides a better opportunity to load lipophilic drugs in high concentrations while allowing for controlled release. These also have the ability to encapsulate water-soluble medicaments in aqueous compartments of surrounding phospholipid layers [38]. Vyas, S. P., Rasika Subhedar, and Sanyog Jain created cationic emulsomes loaded with antiviral medication [zidovudine] using a simple cast film made of solid lipid [trilaurin or tristearin], cholesterol, and soya phosphatidylcholine. The cationic emulsome-based approach demonstrated good intracellular hepatic targeting capabilities, and the strategy could play a critical role in the effective treatment of life-threatening viral illnesses such as hepatitis, HIV, and Epstein-Barr virus infection [39].

Bilosomes

Bilosomes are made up of deoxycholic acid integrated into the niosome membrane. Bile salts are extensively employed by the pharmaceutical industry as penetration enhancers to boost oral bioavailability. Bile salts aid in the membrane stabilization of bilosomes. Bilosomes can improve mucus and oral penetration [40]. Mohamed El-Nabarawi et al. created Bilosomes by encapsulating Daclatasvir in innovative polyethene glycol [PEG] decorated bilosomes [PEG-BILS] in order to obtain better drug delivery to the liver via a thin film hydration approach. Using Design-Expert®

software, various formulation factors on the properties of BILS and the selection of the optimal formulation were developed. In vivo and drug distribution experiments demonstrated that DAC-loaded PEG-BILS delivered more to the liver than DAC-unPEG-BILS and DAC suspension [41].

Ligand-Mediated Approaches for Liver Targeting

Many deadly disorders, such as chronic hepatitis, enzyme insufficiency, and hepatoma, occur in hepatocytes, making the liver an important target tissue for drug administration [Table -2].

Targeting Hepatocytes

Targeting strategies to deliver nanocarriers to the hepatocytes and hepatocellular carcinoma cells have focused primarily on the asialoglycoprotein receptor [ASGP-R]. This method was one of the first and most commonly employed for cell-specific delivery to liver cells. ASGP-R is found in well-differentiated hepatocellular carcinoma cells as well as the membrane of hepatocytes facing sinusoids. This receptor has a high affinity for galactose and N-acetyl-galactosamine residues in a variety of compounds, including lactose, galactoside, galactosamine, and lactobionic acid, which could be attached to the surface of nanocarriers for active targeting [42-44]. When nanocarriers attach to ASGP-R, a complex can form that allows them to enter cells by clathrin-mediated endocytosis [45]. These receptors quickly recycle back to the cell membrane after releasing the ligands inside the cell. Although there are 100 000–500 000 binding sites per cell of ASGP-R on the surface of the liver parenchymal cells, the density and activity of ASGP-R are reduced in the liver under pathological conditions because binding inhibitors in the serum may drastically lower ASGP-R ability [46,47].

Targeting to Hsc Cells

Using the applicable concentrated on ligands conjugated at the floor of nanocarriers, 3 groups of receptors over-expressed on HSCs had been targeted, along with mannose 6-phosphate [M6P]/insulin-like increase component-II receptor, retinol-binding protein [Type VI collagen and integrin] receptors and platelet-derived increase component [PDGF] receptor.4,6 Human serum albumin modified with mannose 6-phosphate [M6P-HAS] companies may be specifically identified by the mannose 6-phosphate/insulin-like increase component II receptor. Retinol binding protein receptors can understand diet A and certain cyclic peptides, ensuing in remarkably enhanced uptake of diet A and cyclic arginine–glycine–aspartate[cRGD] peptide-coupled nanocarriers with the aid of using HSCs [48]. The cyclic peptide C*SRNLIDC*, which has been used in the target delivery, has a unique affinity for the PDGF receptor-b, which can be up-regulated on activated HSCs during hepatic fibrogenesis [49].

Kupffer And Endothelial Cell Targeting

Particular receptors may potentially act as a mediator for uptake by Kupffer cells and sinusoidal endothelial cells. Numerous traits shared by these two types of liver cells are important for targeting delivery systems. Human serum albumin [HAS] and oxidised low-density lipoprotein are specifically recognized by kupffer cells and endothelial cells via scavenger receptors. One of the sugar receptors is a transmembrane protein called the mannose receptor, which is expressed on the surface of macrophages like Kupffer cells and endothelial cells [50,51]. This characteristic has been used to create mannosylated nanocarriers that are specifically targeted at Kupffer cells [52]. There haven't been any reported drug carriers for bile duct epithelial cells, and there haven't been many types of research targeting them. In the future, it may be possible to target the bile duct and cholangiocarcinoma cells using the αvβ6 receptor and the secretin receptor [53-69].

Table 1: Ligand-Mediated Approaches for Liver Targeting

LIVER CELL TYPE	CELLULAR TARGET	TARGETING LIGAND	REFERENCES
Hepatic stellate cells	Mannose- 6-phosphate receptor Type VI collagen receptor PDGF receptor Scavenger receptor class A	Mannose-6-phosphate Cyclic RGD PDGF Human serum albumin	55 56, 57, 58 59 60, 61
Hepatocytes	Asialoglycoprotein receptor	Galactoside	62, 63, 18
		Galactosamine	19
	Plasma membrane fatty acid binding protein (Putative)	Linoleic acid	64
	Scavenger receptor class B type I	Apolipoprotein A-I	65
	Heparan sulfate	Acetyl CKNEKKNKIERNN-KLKQPP-amide	66
	IL-6-receptor and/or immunoglobulin A binding protein (Putative)	Pre-S1	67
	Glycyrrhizin receptors	Glycyrrhizin	22, 25

Sinusoidal endothelial cells	Hyaluronan receptor	Hyaluronan and chondroitin sulfates	68
	Fc receptors	IgG and IgE	69

Conclusion

The development of multi-functional nanosystems for the targeted delivery of drugs, proteins, and nucleic acids to diseased liver cells may be facilitated by advances in material science combined with a better understanding of the anatomy, physiological function, and pathological development of the liver. Carriers must be carefully tailored in order to meet specific objectives including cellular targeting, high loading capacity, protection from nuclease degradation, nanosized, and narrow size distribution because the delivery requirements for each class of treatments vary. The advancements achieved in the creation of synthetic techniques during the past ten years have tremendously aided this process. The creation of polymeric carriers should be the focus of future research. Organocatalytic living ring-opening polymerization [ROP] has provided well-controlled polymerization processes, full biodegradability, and flexibility in adjusting the hydrophobic/hydrophilic and functional block compositions to influence the self-assembly process and enable the incorporation of targeting ligands for the targeted delivery of a variety of therapeutic agents.

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