IJPSR (2013), Vol. 4, Issue 11 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 26 June, 2013; received in revised form, 26 July, 2013; accepted, 25 October, 2013; published 01 November, 2013

LIVER SPECIFIC DRUG TARGETING STRATEGIES: A REVIEW

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Keywords:

Liver, Liver targeting, Liposomes, Phytosomes, Nanocarriers, Vesicular carriers

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ABSTRACT: Drug delivery to liver is one of the most challenging research areas in pharmaceutical sciences. The some physiological barrier such as opsonization, mechanical entrapment by pulmonary vascular bed, uptake by RES represents an insurmountable obstacle for a large number of proteins and drugs, including antibiotics, antineoplastic agents and antiviral agents to target liver disorders. Therefore, various strategies have been proposed to improve the delivery of different drugs to liver and hepatocytes which includes passive accumulation of nanoparticle therapeutics and active targeting by surface modifications of nanoparticles with specific ligands such as carbohydrates, peptides, proteins and antibodies. The present review enlightens about different pathologies of liver and targeting strategies employed in relation to liver anatomy and disease etiologies.

INTRODUCTION: The liver is a vital organ of extreme importance involved in the maintenance of metabolic functions and detoxification of exogenous and endogenous challenges like xenobiotics, drugs, viral infections and chronic alcoholism. Drug induced liver injury is an unresolved problem and often limits drug therapy in clinical practice. Liver diseases, particularly hepatitis B virus infections, liver cirrhosis and hepatocellular carcinoma continue to pose a significant health challenge worldwide due to the lack of curative treatment options besides liver resection and transplantation [1-3]. Nanocarrier therapeutics, which comprises of therapeutic drugs, peptides, proteins or nucleic acids in association with a carrier have size range of 10-200 nm.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.4(11).4145-57

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.4(11).4145-57

They have shown great potentials in their capacities to overcome existing clinical problems[4-6]. They are known to offer significant advantages over free therapeutic agents as their unique size and surface characteristics can:

1. Protect the therapeutic agent, especially for nucleic acids, from premature degradation,
2. Prevent premature clearance and elimination by macrophages of the reticuloendothelial system (res) and by the kidneys,
3. Reduce accumulation of therapeutic agents in tissues other than the liver, thereby limiting undesired organ toxicities,
4. Promote liver cell type specific penetration and uptake and;
5. Overcome mechanisms of drug resistance; with an overall compound effect of enhancing therapeutic safety and efficacy through positive modulations of biodistributions and pharmacokinetic properties [4-7].

Following systemic administration, significant physiological barriers need to be overcome before the successful delivery and uptake of nanocarrier therapeutics by the liver cells can occur. Upon entry into the bloodstream, nanocarrier therapeutics may be subjected to non-specific interactions with serum proteins and the surface deposition of antibodies and/or complement proteins, a process known as opsonization. These two modes of serum protein interactions often act in tandem culminating in the reduction of the overall dose and circulation time of nanocarrier therapeutics via

1. Mechanical entrapment of aggregates in the alveoli capillaries, which typically occurs when the aggregates are larger than 7 µm,[8] and/or;

2. Clearance by resident macrophages of the reticuloendothelial system (RES) in the liver, spleen and bone marrow, especially if the size exceeds 200nm and a large negative surface charge is present.

The endothelial cells lining the liver sinusoids are another component of the RES possessing scavenger receptors that can internalize particles up to 0.23 µm *in vivo* [9]. Nanocarrier therapeutics also has to extravasate through another potential barrier in the form of the liver sinusoidal endothelial wall. Fortunately, as will be seen in the following sections, the physiological and anatomical barriers to hepatic accumulation can be overcome through passive accumulation of nanocarrier therapeutics and active targeting by surface modifications of nanoparticles with specific ligands such as carbohydrates, peptides, proteins and antibodies.

Liver anatomy and physiology [10, 11]: The liver is the largest organ of the body, weighing about 1 to 1.5 kg and representing 1.5 to 2.5% of the lean body mass. The size and shape of the liver vary and generally match the general body shape long and lean or squat and square. The liver is located in the right upper quadrant of the abdomen under the right lower rib cage against the diaphragm and projects for a variable extent into the left upper quadrant. The liver is held in place by ligamentous attachments to the diaphragm, peritoneum, great vessels, and upper gastrointestinal organs. It receives a dual blood supply; approximately 20% of the blood flow is oxygen-rich blood from the hepatic artery, and 80% is nutrient-rich blood from the portal vein arising from the stomach, intestines, pancreas, and spleen. The majority of cells in the liver are hepatocytes, which constitute two-thirds of the mass of the liver. The remaining cell types are Kupffer cells (members of the reticuloendothelial system), stellate (Ito or fat-storing) cells, endothelial cells and blood vessels, bile ductular cells, and supporting structures.

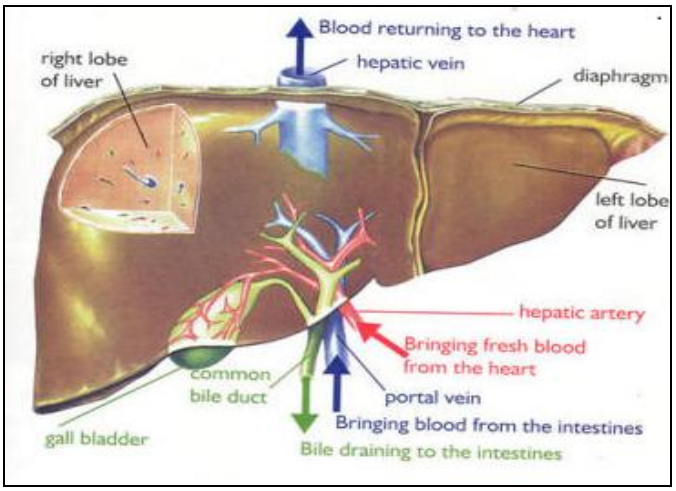

FIG. 1: ANATOMY AND PHYSIOLOGY OF LIVER

Functions of the liver [11, 12]: To maintain the body's metabolic homeostasis and it includes, the efficient uptake of amino acids, carbohydrates, lipids and vitamins and their subsequent storage, metabolic conversion, and release into blood and bile; Synthesis of serum proteins; Hepatic biotransformation of circulating compounds, a process which converts hydrophobic substances into water-soluble derivatives that can be secreted into bile or urine, as well as phagocytosis of foreign macromolecules and particles such as bacteria.

Liver diseases and its treatments: Different types of liver diseases are hepatitis B virus (HBV) infections, liver fibrosis, hepatocellular carcinoma, liver cirrhosis, choleostasis, acute liver failure, nonalcoholic fatty liver disease (NAFLD) and alcoholic liver disease.

Hepatitis B Virus (HBV) Infection: Hepatitis B virus infection is a major global public health problem. HBV infection accounts for 500 000 to 1.2 million deaths each year and is the 10th leading cause of death worldwide. Approximately 2 billion people who have been infected worldwide, more than 350 million are chronic carriers of HBV.

Approximately 15-40% of infected patients will develop cirrhosis, liver failure, or hepatocellular carcinoma (HCC). HBV is a highly contagious DNA virus that is transmitted through parenteral or mucosal exposure to infected blood, serous fluids and other body fluids such as seminal and vaginal fluids. Common routes of infection include perinatal transmission (from an infected mother to infant during birth), unsafe needle sharing, blood transfusion practices and sexual contact [13, 14].

Chronic HBV infection can be divided into three major phases based on virus-host interactions: immune tolerant, immune clearance and inactive carrier phases [15]. The U.S. Food and Drug Administration (FDA) approved anti-HBV drugs can be broadly categorized as interferons (IFN-α2b and pegylated IFN-α2a), nucleoside (lamivudine, entecavir and telbivudine) and nucleotide (adefovir and tenofovir) analogs [16].

Liver fibrosis: Liver fibrosis is defined as the building up of excessive amount of extracellular matrix, also known as scar tissue, in the liver parenchyma[17]. Liver fibrosis is the final pathway for most chronic liver disease and is the main reason for increased mortality in affected patients.

The extent of liver fibrosis displays great individual variation, even after controlling for age (at infection), gender & exogenous factors. Thus, host genetic factors are likely to play an important role in the process of liver scarring [18]. Loss of hepatic functions, ascites, portal hypertension with an increased risk for esophageal varices and HCC are among the most serious complications that are often fatal.

As activation of the hepatic stellate cells (HSCs) is the central event in fibrogenesis, various candidate drugs including rennin-angiotensin system inhibitors, IFN-γ, peroxisomal proliferator activated receptor (PPAR)-γ ligands, pirfenidone, colchicine and herbal medicines that have demonstrated potential in inhibiting HSC activation, proliferation and collagen synthesis have been proposed for the treatment of liver fibrosis. In addition, antioxidants such as vitamin E, silymarin, phosphatidylcholine and S-adenosyl-L-methionine have also been investigated for protection against oxidative stress that may induce hepatic injury and fibrogenesis [19, 20].

Hepatocellular carcinoma (HCC): Hepato-cellular carcinoma (HCC) is the most frequent primary malignancy of the liver and ac- counts for as many as 1 million deaths annually worldwide. In some parts of the world it is the most common form of internal malignancy and the most common cause of death from cancer. El-Serag and Mason I have described an increase of about 80% in the incidence of HCC in the United States over the past 20-30 years and it is estimated that approximately 15,000 new cases occur each year [21]. HCC typically occurs in the milieu of long standing liver diseases such as chronic hepatitis B or C virus infections, alcoholic cirrhosis and non-alcoholic steatohepatitis, the nature of which follows a distinct geographical distribution [22, 23].

In the early stages of HCC, the disease is potentially curable by surgical resection, liver transplantation and nonsurgical local ablation techniques such as percutaneous ethanol injection and radiofrequency ablation (RFA). Patients with advanced HCC can be treated by conventional systemic chemotherapeutic agents such as doxorubicin, cisplatin and 5-fluorouracil, sorafenib used alone or in combination [24-26].

Cholestatic Liver Diseases: Cholestasis (reduced bile duct excretion) is another well-known cause of liver fibrosis. Cholestasis triggers the proliferation of the cholangiocyte lining of the intrahepatic and extrahepatic bile duct systems through a complex regulatory milieu that involves both autocrine and paracrine factors [27]. Cholestasis i.e., blockage of bile flow, is due to either intrahepatic disorders such as cystic fibrosis, granulomatosis or drug side effects. In Cholestasis, the bile canaliculi are enlarged, the fluidity of the canalicular cell membrane is decreased (cholesterol embedding, bile salt effect), their brush border is deformed (or totally absent) and the function of the cytoskeleton, including canalicular motility, is disrupted [28]. The dihydroxy bile acid, ursodeoxycholic acid (UDCA), is increasingly used for the treatment of chronic cholestatic liver diseases.

Liver cirrhosis: Cirrhosis of the liver refers to scarring of the liver which results in abnormal liver function as a consequence of chronic liver injury. Cirrhosis is a leading cause of illness and death in the United States. The most common causes of cirrhosis are excess alcohol use, chronic infection

with hepatitis viruses (such as hepatitis B and hepatitis C), cirrhosis can be caused by other conditions including fatty liver disease, inherited disorders, drug-induced injury, bile duct disorders and autoimmune diseases. A large portion of patients (up to 20%) do not have an identifiable cause for cirrhosis this is known as cryptogenic cirrhosis [29]. Two goals in the management of compensated cirrhosis are;

1. Treatment of the underlying liver disease (e.g., hepatitis C or B, alcohol, non-alcoholic steatohepatitis), and;

2. Prevention or early diagnosis of the complications of cirrhosis.

Acute Liver Failure: Acute liver failure (ALF) is a rare condition in which rapid deterioration of liver function results in altered mentation and coagulopathy in previously normal individuals. U.S. estimates are placed at approximately 2,000 cases per year [30]. The most prominent causes include drug induced liver injury, viral hepatitis, autoimmune liver disease and shock or hypoperfusion; many cases (~20%) have no discernible cause [31]. Acute liver failure often affects young persons and carries a high morbidity and mortality.

The causes of chronic liver failure that is accompanied by fibrosis (cirrhosis) of the liver are; inflammation, chronic persistent viral hepatitis; alcohol abuse, the most common cause in susceptible patients, side effects of drugs such as, folic acid antagonists and phenylbutazone. Liver transplant is the best way to manage the liver failure [32].

Nonalcoholic Fatty Liver Disease (NAFLD): NAFLD and its subtype, Non-Alcoholic Steatohepatitis, or NASH, are usually seen in individuals with metabolic syndrome (MS) or its components such as obesity, type- 2 diabetes (DM), dyslipidemia, and insulin resistance. NASH rarely manifests as inflammation and/or apoptosis/ necrosis only, more often than not it is also accompanied by liver fibrosis [33]. It refers to the accumulation of fat, mainly triglycerides, in hepatocytes so that it exceeds 5% of the liver weight. Treatment strategies for NAFLD have revolved around;

1. Identification and treatment of associated metabolic conditions such as diabetes and hyperlipidaemia;

2. Improving insulin resistance by weight loss, exercise, or pharmacotherapy;

3. Using hepatoprotective agents such as antioxidants to protect the liver from secondary insults.

Alcoholic Liver Disease: Excessive and chronic alcohol consumption is an important causal factor of liver fibrosis and cirrhosis. The process of the breakdown of ethanol produces two profibrotic agents, acetaldehyde and reactive oxygen species (ROS) [17]. Alcoholic liver diseases are often grouped into three histological stages of ALD: fatty liver or simple steatosis, alcoholic hepatitis, and chronic hepatitis with hepatic fibrosis or cirrhosis. These latter stages may also be associated with a number of histological changes including the presence of Mallory's hyaline, mega mitochondria, or perivenular and perisinusoidal fibrosis. Fatty liver develops in about 90% of individuals who drink more than 60 g/day of alcohol, but may also occur in individuals who drink less [34]. Treatment approaches includes inhibition of tumor necrosis factor, antioxidant therapy, stimulation of liver regeneration, and stimulation of collagen degradation.

Drug targeting [35]: Drug targeting is the ability of the drug to accumulate in the target organ or tissue selectively and quantitatively, independent of the site and methods of its administration. Ideally, under such conditions, the local concentration of the drug at the disease site(s) should be high, while its concentration in other non-target organs and tissues should be below minimal level to prevent any negative side-reactions.

The following advantages of drug targeting are:

1. Drug administration protocols may be simplified;

2. Drug quantity required to achieve a therapeutic effect may be greatly reduced;

3. The cost of therapy reduced;

4. Drug concentration in the required sites can be sharply increased without negative effects on non-target compartments. The same is, for the great extent, true for the use of many diagnostic agents.

Currently, the concept of magic bullet includes a coordinated behavior of three components:

i) Drug;

ii) Targeting moiety and;

iii) Pharmaceutical carrier used to multiply the number of drug molecules per single targeting moiety.

Pharmaceutical carriers include soluble polymers, microcapsules, microparticles, cells, cell ghosts, lipoproteins, liposomes, and micelles. All of them can be made targeted in one way or another.

The recognition of the target can occur on the level of a whole organ, on the level of certain cells specific for a given organ, or even on the level of individual components characteristic of these cells, such as cell surface antigens. The most universal form of target recognition is the recognition on the molecular level, based on the fact that every organ or tissue certain compounds (antigens) can be found that are specific only for the organ of interest.

For successful targeting, another compound can be used as a transporting unit, which is capable of the specific interaction with the specific target component (for example, a monoclonal antibody against the target antigen). Basing on this principle, numerous systems for drug targeting have been constructed capable of the delivery of pharmaceuticals to the variety of tissues and organs.

Currently, the whole set of targeting protocols is under development that includes many different approaches to targeted drug delivery. Not necessarily these approaches involve the use of specific targeting moieties. In certain cases various physical principles and/or some physiological features of the target area may be utilized for a successful targeting of pharmaceuticals and pharmaceutical carriers.

Principal schemes of drug targeting currently investigated in various experimental and clinical settings include

a. Direct application of the drug into the affected zone (organ, tissue);

b. Passive accumulation of the drug through leaky vasculature (tumors, infarcts, inflammation);

c. Physical targeting based on abnormal pH and/or temperature in the target zone, such as tumor or inflammation (pH and temperature-sensitive drug carriers);

d. Magnetic targeting of drugs attached to paramagnetic carriers under the action of external magnetic field;

e. Use of vector molecules possessing high specific affinity toward the affected zone.

Liver targeting: The liver is a critical target tissue for drug delivery because many fatal conditions including chronic hepatitis, enzyme deficiency, and hepatoma occur in hepatocytes.

In general, liver targeting systems employ passive trapping of microparticles by reticuloendothelium or active targeting based on recognition between hepatic receptor and ligand-bearing particulates [36].

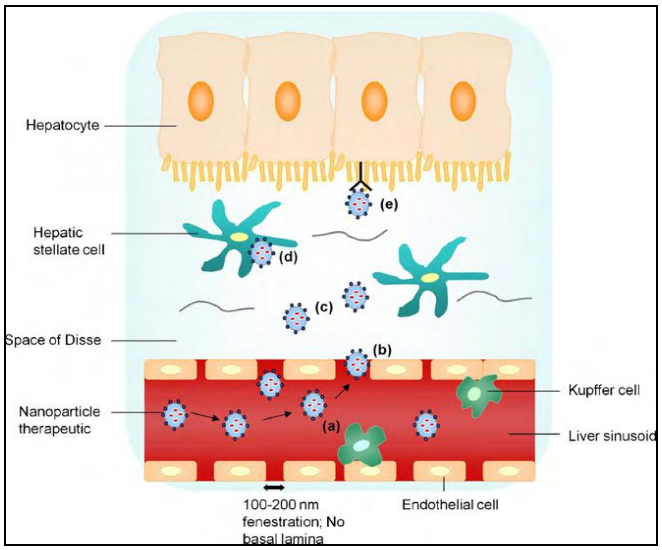

FIGURE 2: PASSIVE AND ACTIVE LIVER TARGETING STRATEGIES OF NANOPARTICLE THERAPEUTICS [37]

Passive targeting: Passive targeting refers to NP transport through leaky tumor capillary fenestrations into the tumor interstitium and cells by passive diffusion or convection or also refers to the accumulation of nanoparticle therapeutics at a specific body site due to certain anatomic or pathophysiological features [38]. The liver sinusoids are highly specialized capillaries characterized by:

1. the presence of 100-200 nm fenestrations along the endothelial wall and;

2. Absence of basal lamina. As a result of these characteristics, rapid and passive liver accumulations are frequently observed with nanoparticle therapeutics following intravenous (i.v) administration.

Following systemic administration, the defining size properties (typically < 200nm in diameter) of nanoparticle therapeutics greatly facilitates passive liver targeting in the absence of significant self-aggregation or aggregation with serum proteins as it allows for their extravasation through the slightly larger sinusoidal fenestrations. This effectively builds up a high local concentration of nanoparticle therapeutics in the space of Disse, where diffusion to the various liver cell types can occur.

Interestingly, evidence has also suggested an opportunity for deformable nanocarriers of up to 400 nm to extravasate through the sinusoid endothelial fenestrations via a mechanism of forced extrusion, possibly aided by transient interactions with the sinusoidal endothelial cells[39]. In HCC, passive accumulation of nanoparticle therapeutics in the liver can also be achieved by EPR effect that was first described by Matsumura and Maeda in 1986 [40].

The EPR effect can be observed in almost all human cancers with the exception of hypovascular tumors like prostate cancer or pancreatic cancer. For such a passive targeting mechanism to work, the size of the nanoparticles must be controlled to avoid uptake by the reticuloendothelial system (RES). The EPR effect stems from distinctive features of the tumor microenvironment including:

1. Leaky tumor vasculature brought about as a consequence of the rapid and incomplete tumor angiogenesis to meet the elevated demands for oxygen and nutrients, leading to enhanced permeability and extravasation of macromolecules, and;

2. Impaired lymphatic drainage, which favors the retention of nanoparticle therapeutics in the tumor tissues [41].

As the size of the gap junction between endothelial cells is reported to vary between 400 and 600 nm, nanoparticle therapeutics are therefore expected to be extremely efficient at extravasating from the tumor microvasculature to result in a high local tumor interstitial concentration. Indeed, the EPR effect has been credited with the selective deposition and targeting of zein nanoparticle (ZP) encapsulated 5-fluorouracil in HCCs following intravenous injection. In these studies, the drug loaded ZPs could be efficiently targeted at the liver by intravenous delivery observed in patients with liver cancer [42].

The method and site of administration of nanoparticle therapeutics are also known to influence distribution patterns within the liver. In the area of gene delivery, for instance, hydrodynamic injections of naked DNA led to increased accumulations of DNA in the livers of rodents as the increased intrahepatic pressure results in a transient increase in the diameter of the sinusoidal fenestrate to cause a leakage of DNA-containing solutions from hepatic sinusoids into the space of Disse [9].

Active targeting: The specific delivery of the therapeutic system to the diseased cell type allows for the capitalization of the therapeutic effects of the cargo and also minimizes unwanted side effects on normal liver cells resulting from non-specific cellular uptake. The diverse physiological functions of the human liver are achieved through the specific activities of various cell types, including the non-parenchymal sinusoidal endothelial cells (SECs), Kupffer cells (KCs), hepatic stellate cells (HSCs) and the predominant parenchymal hepatocytes. In liver fibrosis, HSCs are considered to be the main target for therapeutic interventions due to their major roles in the secretion and maintenance of copious amounts of extracellular matrix (ECM) in response to various biochemical stimuli produced by the injured hepatocytes, SECs and KCs.

Hepatocytes, on the other hand, are implicated in the development of HBV infections and HCC and therefore, are being targeted for the treatment of these diseases. As each of the two liver cell types has distinct morphologies, physiological activities and pathoanatomical characteristics that are reasonably established, unique targeting opportunities of therapeutics by ligand-mediated approaches to the HSCs and hepatocytes are abound.

TABLE 1: LIGAND MEDIATED APPROACHES FOR LIVER TARGETING

Liver cell type	Cellular target	Targeting ligand	References
Hepatic stellate cells	Mannose – 6 –phosphate receptor	Mannose-6-phosphate	44
	Type VI collagen receptor	Cyclic RGD	45, 46, 47
	PDGF receptor	PDGF	48
	Scavenger receptor class A	Human serum albumin	49, 50
Hepatocytes	Asialoglycoprotein receptor	Galactoside	51, 63, 67
		Galactosamine	68
	Plasma membrane fatty acid binding protein (Putative)	Linoleic acid	54
	Scavenger receptor class B type I	Apolipoprotein A-I	55
	Heparan sulfate	Acetyl CKNEKKNKIERNNKLKQPP-amide	56
	IL-6-receptor and/or immunoglobulin A binding protein (Putative)	Pre-S1	57
	Glycyrrhizin receptors	Glycyrrhizin	58, 62

RGD: Arg-Gly-Asp; PDGF: platelet-derived growth factor.

Drug targeting to Hepatic stellate cells (HSCs): The five main strategies make the use of features of the pathological development of liver fibrosis that is initiated by the activation, proliferation and the subsequent transformation of HSCs into myofibroblasts. Activated HSCs are known to have upregulated expression of mannose-6-phosphate/ insulin-like growth factor II (M6P) receptors to facilitate the activation of the cytokine, transforming growth factor β (TGF-β), which stimulates collagen production by HSCs [43].

Capitalizing on this phenomenon, the direct conjugation of M6P via a short peptide linker to a N-(2- hydroxypropyl) methacrylamide (HPMA) copolymer showed a majority uptake (~80%) by the HSCs in dimethylnitrosamine (DMN)-induced liver fibrotic rats [44]. To exploit native interaction between collagen type VI receptors and its ligand, researchers have covalently attached a cyclic octapeptide C*GRGDSPC* (C* denotes the cyclizing cysteine residues) to the lysine groups of human serum albumin (HSA) and observed selective internalization by activated rat HSCs [45]. A further modification was made to the peptide by substituting cysteine with lysine (C*GRGDSPK*) in order to replace the less stable cyclizing disulfide (—S—) bond with a more stable peptide bond (—NH—CO—) in the latter, without adversely influencing targeting efficacy [46, 47]

Receptors for platelet-derived growth factors (PDGFs), which mediate many of the HSC responses to cytokines, are generally upregulated during liver injury. Expression of the PDGF receptor type, in particular, is acquired at high levels during the myofibroblastic transformation of HSC [48]. The scavenger receptors (ScRs) present on HSCs act as an alternative endocytotic uptake route for nanoparticle therapeutics, particularly for the HSA-based therapeutic systems due to their polyanionic nature [49, 50].

Drug targeting to Hepatocytes: Targeting to the asialoglycoprotein receptor (ASGP-R) is the most universally employed method to enhance clathrin mediated endocytotic uptake of nanoparticle therapeutics by hepatocytes. This approach takes advantage of the innate binding affinity of the ASGP-R to a broad range of molecules exposing galactose and N-acetyl-galactosamine residues, such as asialoorosomucoid, asialofetuin (AF), sterylglucoside, lactose and poly-(N-ρ-vinylbenzyl-O-β-Dgalactopyranosyl-[1- 4]-D-glucosamine (PVLA) for target in to hepatocytes.

In polymeric systems, the most commonly seen approach is through coupling of lactobionic acid or lactose to the nanocarrier through carbodiimide chemistry, with the final product retaining functional galactose moieties.

L. Li and his group has recently synthesized a series of amphiphilic polycarbonate-based copolymers bearing carbohydrate pendant chains as targeted drug carriers and found significantly higher uptake of doxorubicin (DOX)-loaded galactose-containing micelles by the ASGP-R positive HCC cell line HepG2 compared to the ASGP-R negative HEK293 cell line [51].

The specificity of galactose-mediated uptake of the DOX-loaded nanoparticles by HepG2 was evidenced by the inhibition by AF in a dose-dependent manner. Interestingly, although the conjugation of most galactose-bearing moieties to the polymer backbone occur at the 1-position of the pyranose ring, Li and his co-workers results demonstrated that the ASGP-R can recognize galactopyranosides appended at the 6-position. Simultaneous expression of ASGP-Rs in normal hepatocytes and HCC cells, however, could restrict the clinical applicability of this class of receptors for targeting purposes.

In fact, studies have discovered a decrease in ASGP-R expression in HCC, particularly in the poorly differentiated state [51, 52], suggesting that the normal hepatocytes may internalize the nanoparticle therapeutics to a greater extent compared to their diseased counterparts. The tumor levels of the galactosylated poly (HPMA)-DOX is nevertheless substantially higher than the background levels, implying that the galactose moiety does provide some form of targeting, albeit with lower specificity, to the tumors. The fatty acid metabolism and cholesterol storage function of the liver is another avenue that has been explored to enhance hepatocyte uptake of nanoparticle therapeutics. For example, linoleic acid, an essential polyunsaturated fatty acid that is taken up by hepatocytes via its putative plasma membrane transporter [53] has been used to drive the uptake of self-assembled superparamagnetic iron oxide nanoparticles-loaded chitosan-linoleic acid/DNA complexes by hepatocytes for imaging and gene delivery purposes [54].

Additionally, various liposomes containing apolipoprotein A-I (apo A-I), the major protein of the high-density lipoprotein (HDL), have exploited the natural mechanism of uptake of HDL cholesteryl ester via the class B type I scavenger receptor, CLA-1 (human) or SR-BI (rat) to enhance internalization in the hepatocytes [55].

Besides the frequently over expressed cell surface receptors such as transferrin, folate and epidermal growth factor receptors in solid tumors, other ligand mediated targeting strategies have also exploited natural hepatic invasion mechanisms by protozoa through the use of acetyl-CKNEKKNKIERNNKLKQPP-amide to bind to heparin sulfate proteoglycans on the hepatocyte surface [56] and the use of pre-S1, a hepatitis B viral envelope protein sequence known to mediate virus entry into hepatocytes [57]. In addition, the hepatic glycyrrhizin (GL) receptors have also been targeted through GL surface modifications [58].

Liver targeting drug carriers:

TABLE 2: LIVER TARGETING DRUG CARRIERS

Carriers	Model drug	Polymers/ lipids	Method	References
Liposome	30-stearyl glycyrrhizin	HEPC,CH	Ether Injection	62
	Probucol	DSPC, CH	Ether Injection	63
Nanoparticles	Oridonin	BSA	Desolvation	67
	Adriamycine	Chitosan	Ionic gelation	58
	Antifibrotic drug	HAS	Desolvation	45
	Paclitaxel	γ-PGA-PLA	Emulsion/solvent evaporation	68
	Norcantharidin	Chitosan	Ionic gelation	69
	5-fluorouracil	Zein	Phase separation	42
Polymeric micelles	Diammonium glycyrrhizinate	Chitosan	-	70
Phytosome	Silymarin	Phospholipids	Solvent evaporation	73

HEPC: hydrogenated egg phosphatidylcholine; CH: cholesterol;
DSPC: Distearoylphosphatidylcholine; γ-PGA-PLA: poly (γ-glutamic acid)-poly (lactide);
BSA: Bovine serum albumin; HSA: Human serum albumin.

Liposomes: Liposomes are small vesicles composed of unilamellar or multilamellar phospholipid bilayers enclosing an aqueous space. Soluble drugs can readily be incorporated into this aqueous space and lipophilic drugs can be incorporated into the lipid bilayers. Elimination from the circulation is dependent on the lipid composition, charge, and size of the liposomes. Common liposomes such as neutral and negatively-charged liposomes, are however, primarily cleared by the phagocytotic processes of the cells of the reticuloendothelial system (RES), the KCs having the greatest responsibility for this process.

It has been shown for instance that the targeting of cytostatic agents such as adriamycine to tumours is associated with loss of KC function, thereby contributing to the immuno-suppressed status of patients. The high KC uptake has been surprisingly under-exploited in drug targeting approaches to treat liver diseases [59]. Liposomes have been used for the targeting of anti-Leishmania drugs [60] and immunomodulators [61] and have greatly increased the efficacy of these drugs in Leishmania infections and metastatic tumour growth, respectively.

Hepatocyte selective targeting of liposome can be achieved through introduction of cells recognizing ligands on the liposomal surface. There is galactose receptor on the surface of hepatocytes which recognizes the galactosyl residues of desilated serum glycoproteins. So, galactose-terminated compound such as asialofetuin lactosylceramide have been used as the ligand on liposomes for targeting to hepatocytes [62]. M. Hashida and his co-workers synthesized the galactosylated liposomes for hepatocyte targeting and elucidate the relationship between the movements of galactosylated liposomes [63]. The glycyrrhizin derivative is also used as the ligand on liposome for targeting to hepatocytes.

H. Kiwada and his co-workers developed the glycyrrhizin modified liposome for hepatocyte targeting [62]. PEG liposomes, also called stealth liposomes because when modifying the SUV liposome membrane by adding polyethylene glycol can markedly reduce the interaction of the vesicles with the stationary macrophages in the liver and spleen after i.v. application and this increases the circulation half-time.

Pohlen *et al* prepared the 5-flurouracil enclosed in Stealth Liposome for the treatment of Liver Metastases [64].

Nanoparticles (NPs): Biodegradable nanoparticles (NPs) are effective drug delivery devices. Various polymers have been used in drug delivery research as they can effectively deliver the drug to a target site and thus increase the therapeutic benefit, while minimizing side effects [65]. The controlled release (CR) of pharmacologically active agents to the specific site of action at the therapeutically optimal rate and dose regimen has been a major goal in designing such devices. Liposomes have been used as potential drug carriers instead of conventional dosage forms because of their unique advantages which include ability to protect drugs from degradation, target the drug to the site of action and reduce the toxicity or side effects [66].

However, developmental work on liposomes has been limited due to inherent problems such as low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components and poor storage stability. On the other hand, polymeric NPs offer some specific advantages over liposomes. For instance, NPs help to increase the stability of drugs/proteins and possess useful CR properties. Nanoparticles generally vary in size from 10 to 1000 nm. In the NPs drug is dissolved, entrapped, encapsulated or attached to a NPs matrix and depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained.

For targeting of polymeric nanpoarticle to liver various ligands such as folic acid and asialoglycoproteins, galactosyl residues, glycyrrhizin derivative, have been introduced into drug carriers. C. Li *et al* designed albumin nanoparticles with surface modification by galactose residues to achieve the effectively targeting delivery of Oridonin into liver cancer cells [67].

Ping *et al* conjugated glycyrrhizin (GL) to the surface of chitosan nanoparticles (CS-NPs), prepared by an ionic gelation process [58]. These nanoparticles were developed for a drug delivery system targeting the liver through a specific interaction between GL and hepatocytes.

The cellular uptake of GL-CS-NPs was dependent on incubation time and dose of nanoparticles, suggesting that internalization of these nanoparticles into hepatocytes was mostly mediated by a ligand receptor interaction. Liang *et al* prepared Paclitaxel-loaded poly (γ-glutamic acid)-poly (lactide) nanoparticles as a targeted drug delivery system for the treatment of liver cancer and they studied, the distribution of the particle size, the zeta potential, the drug loading content and the drug loading efficiency of the prepared nanoparticles, and their release profile and cytotoxicity on HepG2 cells (a liver cancer cell line) were investigated *in vitro* [68].

Additionally, biodistributions of the prepared nanoparticles were studied *in vivo* in normal mice and hepatoma-tumor-bearing nude mice. Q. Wang *et al* developed Norcantharidin-associated galacto-sylated chitosan nanoparticles for hepatocyte-targeted delivery and confirm its targeting characteristics [69].

Polymeric micelles: Polymeric micelles have recently emerged as a novel promising colloidal carrier for the targeting of poorly water soluble and amphiphilic drugs. Polymeric micelles are considerably more stable than surfactant micelles and can solubilize substantial amounts of hydrophobic compounds in their inner core. Due to their hydrophilic shell and small size they sometimes exhibit prolonged circulation times *in vivo* and can accumulate in tumoral tissues. Polymeric micelles also used in liver targeting, Yang KW and his co-worker designed Diammonium glycyrrhizinate (DG)-loaded conventional PIC micelles (mPIC micelles) and lactose-modified PIC micelles (Lac-PIC micelles) and they found that Lac-PIC micelles could deliver more DG to liver than mPIC micelles [70].

Phytosomes: The term "Phyto" means plant while "some" means cell-like. The phytosome structures contain the active ingredients of the standardized plant extract or its constituents bound to phospholipids, mainly phosphatidylcholine producing a lipid compatible molecular complex. Phytosomes have improved pharmacokinetic and pharmacological parameter which in result can advantageously be used in the treatment of the acute and chronic liver disease of toxic metabolic or infective origin or of degenerative nature. It can also be used in anti-inflammatory activity as well as in pharmaceutical and cosmetic compositions[71]. Phytosomes are prepared by reacting the herbal extract in an aprotic solvent such as methylene chloride, dioxane and ethyl acetate with the phospholipid such as phosphatidylcholine, phosphatidylethanolamine or phosphatidyiserine dissolved in the same solvent. After solubilization has been completed, the complex compounds are isolated by removing the solvent under vacuum, by freeze drying or by precipitation with non-solvents such as n-hexane.

Thus, the obtained complexes are lipophilic in character and soluble in a polar and aprotic solvent, in which the individual components of the complex are normally insoluble[71]. The phytosome process has also been applied to many popular herbal extracts including *Ginkgo biloba,* grape seed, hawthorn, milk thistle, green tea, and ginseng. The flavonoid and terpenoid components of these herbal extracts lend themselves quite well for the direct binding to phosphatidylcholine [72]. Ravarotto *et al* reported silymarin phytosome show better antihepatotoxic activity than silymarin alone and can provide protection against the toxic effects of aflatoxin B1 on performance of broiler chicks [73].

CONCLUSION: Advances in material science, coupled with a greater understanding of the anatomy, physiological function and pathological progression of the liver, could lead to the development of multi-functional nanosystems for the targeted delivery of drugs, proteins and nucleic acids to the diseased liver cells. Given that the delivery requirements for each class of therapeutics is different, so carriers have to be highly optimized in order to fulfill specific needs such as cellular targeting, high loading capacity, protection from nuclease degradation, nanosize and narrow size distribution.

This process has been greatly facilitated by the progress made in the development of synthetic methodologies over the past decade. Future research work should be aimed at to the synthesis of polymeric carriers, organocatalytic living ring opening polymerization (ROP) has conferred well-controlled polymerization processes, full bio-degradability, and flexibility in adjusting the hydrophobic/hydrophilic and functional block compositions to influence the self-assembly

process and allow for the incorporation of targeting ligands for the specific delivery of a wide range of therapeutic agents.

ACKNOWLEDGEMENT: Authors thanks Hon. Prof. M. N. Navale, Founder President, Sinhgad Technical Education Society, Pune, for providing digital library for referencing.

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How to cite this article:
Gorad RS, Mandlik SK and Gujar KN: Liver specific Drug Targeting strategies: A Review. *Int J Pharm Sci Res* 2013; 4(11): 4145-57. doi: 10.13040/IJPSR. 0975-8232.4(11).4145-57