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A Review on Hepatic Targeting Drug Delivery System

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ABSTRACT

Treatment of liver carcinoma, other liver diseases, and drug delivery to the liver are challenging tasks for researchers within the pharmaceutical field. Some physiological barrier like opsonization, mechanical entrapment by the pulmonary vascular bed, uptake by RES represents an insurmountable obstacle for an oversized number of proteins and medicines, including antibiotics, antineoplastic agents, and antiviral agents to focus on liver disorders. Therefore, various strategies are proposed to boost the delivery of various drugs to liver and hepatocytes which has a passive accumulation of nanoparticle and active targeting by surface modifications of nanoparticles with specific ligands like carbohydrates, peptides, proteins, and antibodies. This review enlightens about different pathologies of the liver and ligand-mediated approaches for liver and formulation aspects of liver targeting of drugs.

INTRODUCTION

Site-specific drug delivery or targeted drug delivery system has the potential to increase local drug concentrations and thereby increase the effectiveness of the medicines with fewer side effects. Liver diseases especially disease are one in every of the foremost prevalent cancers, which high mortality. Because of the high toxicity and poor specificity of the chemotherapeutic agents, this method of treatment sometimes ends in systemic toxicity and adverse effects that are harmful to the patient. Targeted drug deliveries are often a highly desirable strategy to boost the therapeutic outcome, with significantly decreased toxic side-effects compared to traditional chemotherapy. The recent strategies use site-specific drug carriers like antibodies, peptides, natural and modified, or synthetic polymers. Some prodrugs gain cell specificity whereas others gain specificity by using cell-specific surface receptors (e.g., steroid transporter) that facilitate prodrug transport into liver cells. Various strategies are proposed to spice up the delivery of various drugs to liver and hepatocytes which has a passive accumulation of nanoparticle therapeutics and active targeting by surface modifications of nanoparticles with specific ligands like carbohydrates, peptides, proteins, and antibodies.

The liver could even be vitals of maximum importance involved within the upkeep 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 sometimes limits drug therapy in clinical practice. Liver diseases, particularly hepatitis B virus infections, liver cirrhosis, and hepatoma still pose a significant health challenge worldwide due to the dearth of curative treatment options besides liver resection and transplantation. [1] They have shown great potentials in their capacities to beat existing clinical problems they're known to supply significant advantages over free therapeutic agents as their unique size and surface characteristics can:

- Protect the therapeutic agent, especially for nucleic acids, from premature degradation,
- Prevent premature clearance and elimination by macrophages of the RES (res) and by the kidneys,
- Reduce the accumulation of therapeutic agents in tissues except for the liver, thereby limiting undesired organ toxicities,
- Promote liver cell-type-specific penetration and uptake.

Drug targeting to the liver may represent such a replacement strategy; it seems clear that the drugs do accumulate rapidly in the liver; they simply don't accumulate within the correct intrahepatic cell-type. The target cell for therapeutic intervention varies with the disease. In hepatitis or non-alcohol-induced hepatitis (NASH), the hepatocyte is that the designated target cell, in acute liver inflammation it is the Kupffer or the endothelial cell, in liver fibrosis or cirrhosis it is the hepatic stellate cell, in primary biliary cirrhosis it is the canal vegetative cell and in cancer of the liver, it is the tumor cell that is the key target cell for therapeutic interventions. This review describes the drug delivery in the targeted site and recovery of diseases. Till today some delivery systems are marketed as liver targeted drug delivery systems. [1]

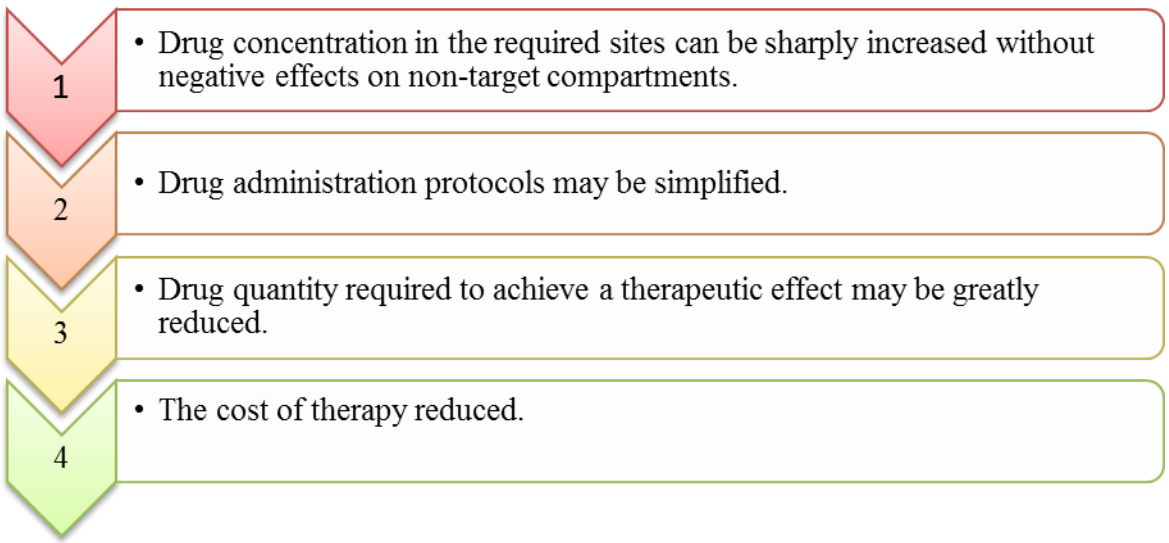
LIVER DISEASES

Differing kinds of liver diseases are hepatitis B virus (HBV) infections, liver fibrosis, carcinoma, liver cirrhosis, cholestasis, acute liver failure, non-alcoholic liver disease (NAFLD), and alcoholic disease.

DRUG TARGETING

Drug targeting is the ability of the drug to accumulate within the organ or tissue selectively and quantitatively, independent of the positioning and methods of its administration. Ideally, under such conditions, the non-targeted site contains a low concentration of drugs and the targeted site contains a high level of drug concentration at the same time.

Advantages of drug targeting



LIVER TARGETING DRUG DELIVERY

The liver may be a critical target tissue for drug delivery because many fatal conditions including enzyme deficiency, chronic hepatitis, and hepatoma occur in hepatocytes. In general, liver targeting systems employ active targeting supported recognition between ligand-bearing particulates and hepatic receptor or passive trapping of microparticles by reticulo endothelium.

PASSIVE AND ACTIVE LIVER TARGETING

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 build-up of nanoparticle therapeutics at a selected body site because of certain anatomic or pathophysiological features. [2]

Active targeting:

The particular delivery of the therapeutic system to the diseased cell type allows for the capitalization of the therapeutic effects and also minimizes unwanted side effects on normal liver cells resulting from non-specific cellular uptake. The varied physiological functions of the human liver are achieved through the particular activities of varied cell types, including the non-parenchymal sinusoidal endothelial cells (SECs), Kupffer cells (KCs), hepatic stellate cells (HSCs), and also the predominant parenchymal hepatocytes. In liver fibrosis, HSCs are considered to be the most targets for therapeutic interventions thanks to their major roles within the secretion and maintenance of copious amounts of extracellular matrix (ECM) in response to numerous biochemical stimuli produced by the injured hepatocytes, SECs and KCs. [3]

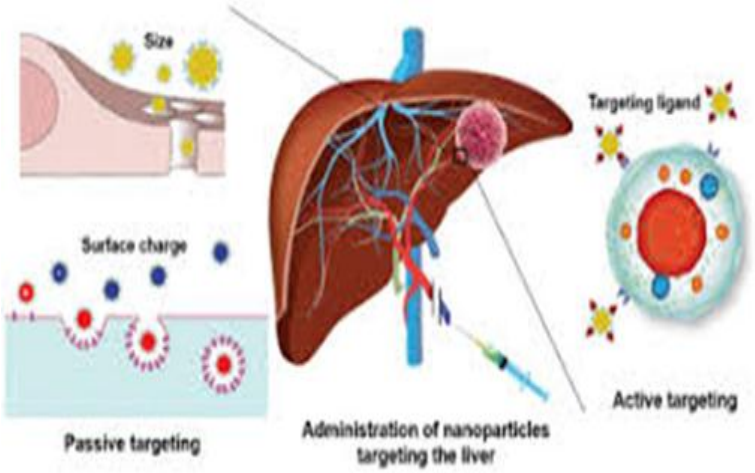


Figure No. 1: Passive and active targeting strategies

Drug targeting to hepatic stellate cells (HSCs)

The main strategies make the utilization of features of the pathological development of liver fibrosis that's initiated by the activation, proliferation, and therefore the subsequent transformation of HSCs into myofibroblasts. Activated HSCs are known to possess an upregulated expression of mannose-6-phosphate/ insulin-like protein II (M6P) receptors to facilitate the activation of the cytokine and remodeling protein β (TGF-β), which stimulates collagen production by HSCs. HSC, which comprise about 5–10% of the complete amount of liver cells, play a pivotal role in cirrhosis. This disease, which is that the end stage of a perpetuating fibrotic process within the liver is also a chronic disease that greatly disturbs the normal liver architecture, alters liver perfusion, and eventually affects all liver functions.

Patients with cirrhosis have a subsequent risk for hepatoma.The main causes of cirrhosis are chronic viral hepatitis or C infections, substance abuse, biliary problems, and steatohepatitis. The fibrotic process is that the final common pathway of these different liver diseases. particularly the rise within the incidence of hepatitis B and C infections and also the increase in obesity resulting in fatty livers are the reason for a worldwide increase within the. Incidence of liver fibrosis and cirrhosis.

The chronic damage within the liver results in loss of hepatocyte activity and functioning. Factors generated by the damaged hepatocytes and activated non- parenchymal cells subsequently induce activation, transformation, and proliferation of fibroblast-like cells (hepatic stellate cells and portal fibroblasts) and these cells successively produce excessive amounts of connective tissue (extracellular matrix proteins like collagen types I and III)

forming a fibrous scar. Eventually, this ends up in malignant hypertension thanks to the increased intrahepatic resistance.

This increased portal pressure represents one amongst the key clinical problems because it ends up in variceal bleeding, one in every of the foremost life-threatening complications in cirrhotic patients. A complicating considers the management of high portal force per unit area is that the reduced mean blood pressure in these patients. Treatment of the air mass within the vena portae without affecting the systemic force per unit area represents a significant challenge and requires cell-selective approaches. Selective delivery of gas donor prodrugs to the liver and intrahepatic delivery of genes encoding for NO synthesizing enzymes are explored but to this point without clinical success. [4]

Drug targeting to Hepatocytes

For several diseases, hepatocytes represent the foremost relevant target cell. Hepatocytes play a vital role in liver diseases like viral hepatitis(Hepatitis A, B, or C) alcohol-induced steatohepatitis (ASH), non-alcohol-induced steatohepatitis (NASH), some genetic diseases like hepatolenticular degeneration, hemochromatosis, and several other metabolic disorders. Altogether these cases, hepatocytes are infected or damaged and as a consequence, they initiate the disease activity. Drug uptake by this particular cell-type is generally not a serious issue thanks to the primary pass effect and therefore the presence of the many transporters and endocytotic receptors that take up drugs. Nevertheless, to boost the therapeutic effects (in case of hepatoma, hepatitis, and just in case of gene-based therapies) or to scale back side-effects of medicine (in case of as an example antiviral or anticancer drugs) many methods for hepatocyte-selective drug targeting are explored within the past decades.

ESSENTIAL ELEMENTS FOR DESIGNING DELIVERY SYSTEMS FOR LIVER TARGETING

- Ensures that such interactions happen only with within the desired anatomical location of the liver; therefore, it must fulfill the subsequent criteria:

- It must be able to cross the anatomical barriers like those of stomach and intestine,

- Should be recognized selectively by the receptor present on the liver cell-like asialoglycoprotein,

➢ The fabricated delivery system must be non-toxic, biocompatible, biodegradable, and physicochemically stable within the liver cells either *in-vivo* or *in-vitro.*

➢ It should have uniform sinusoid capillary distribution,

➢ Should have a controllable and predictable rate of drug release to the liver cells,

➢ Drug release shouldn't affect the drug distribution.

➢ It should show minimal drug leakage during its passage through the stomach, intestine, and other parts of the body,

➢ The carrier used for encapsulating the herbal drugs must be eliminated from the body without imparting any sign of toxicity and no carrier should induce modulation of a diseased state.

➢ The preparation method of the drug delivery system should be easy or reasonably simple, reproducible, and cost-effective.

LIVER TARGETING DRUG CARRIERS

❖ **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 are often incorporated into the lipid bilayers. Elimination from the circulation depends on the lipid composition, charge, and size of the liposomes. Common liposomes like neutral and negatively-charged liposomes, primarily cleared by the phagocytotic processes of the cells of the system (RES). Hepatocyte selective targeting of liposome is often achieved through the introduction of cells recognizing ligands on the liposomal surface. There's a galactose receptor on the surface of hepatocytes which recognizes the galactosyl residues of desolated serum glycoproteins. So, a galactose-terminated compound like asialofetuin lactosylceramide is used because of the ligand on liposomes for targeting to hepatocytes.

❖ **Nanoparticles (NPs):**

Biodegradable nanoparticles (NPs) are effective drug delivery devices. Various polymers are employed in drug delivery research as they'll effectively deliver the drug to a target site and

thus increase the therapeutic benefit while minimizing side effects. The controlled release (CR) of pharmacologically active agents to the actual site of action at the therapeutically optimal rate and dose regimen has been a significant goal in designing such devices.

Various ligands like folate and asialoglycoproteins, galactosyl residues, glycyrrhizin derivative, are introduced into drug carriers for targeting to the liver. C. Li et al designed albumin nanoparticles with surface modification by galactose residues to comprehend the effectively targeting delivery of Oridonin into cancer of the liver cells. [5]

❖ **Phytosomes:**

Phytosomes have improved pharmacokinetic and pharmacological parameters which in result can advantageously be utilized within the treatment of the acute and chronic disease of toxic metabolic or infective origin or of degenerative nature. Phytosomes are prepared by reacting to the herbal extract in an aprotic solvent like chloride, dioxane, and ester with the phospholipid like phosphatidylcholine, phosphatidylethanolamine, or phosphatidylserine dissolved within the identical 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 like n-hexane. [6]

❖ **Treating carcinoma with glass beads**

Treating carcinoma with tiny radioactive glass beads could be a new method that has been recently introduced. during this treatment, radioactive glass beads are injected into the most artery which supplying blood to the liver. the beads entered into the liver, where they deliver localized radiation to malignant cells in liver tumors.[7]

❖ **Tethering bile acids**

Another approach for targeting cancer of the liver is that the use of bile acids, which are efficiently obsessed with hepatoma cells via sodium– independent transport carriers. A series of bile acid–platinum conjugates are synthesized by a suitable method and their cytotoxicity investigated both in vivo and in vitro manner. Conjugate Bamet–UD2 exhibited enhanced uptake in hepatocytes and has the ability the same as that of cisplatin to inhibit tumor growth and the tendency to prolong survival time.[8]

❖ **Chylomicron emulsion**

lipoproteins are the Natural spherical macromolecular emulsion particles these are involved in intercellular lipid and cholesterol transport within the circulation.[9] Chylomicrons are triglyceride-rich lipoprotein emulsions, dietary lipids absorbed through the intestine membrane into blood circulation are packed into chylomicrons. Lipase could also be a lipoprotein enzyme that could hydrolyze the core triglycerides of the chylomicron in blood circulation. On the surface of the chylomicron, many alternative apolipoproteins are anchored by their receptors these modified chylomicrons are haunted by liver parenchymal cells. When chylomicrons are reconstituted by natural lipids (100nm) was preferentially haunted by liver hepatocytes. When a drug is incorporated into chylomicron emulsion it should be easily targeted to the liver. The drug inside the emulsion is chemically more stable than a free drug because it's shielded from enzymatic degradation. Also, the drug shows significant release when it's inside a chylomicron emulsion.Nucleoside analog iododeoxy– uridine was successfully delivered by recombinant chylomicrons to specialize in liver parenchymal cells for serum hepatitis treatment. it had been delivered encapsulated therapeutics in higher concentrations in the liver.

❖ **Magnetoliposomes**

It is a unique drug delivery carrier system. Generally used anticancer drugs exhibit severe side effects that limit their effective therapeutic use.[10] Magnetoliposome is an approach to increase the beneficial/adverse effect ratio of such drugs, which is used to target diseased organs or tissues by employing a field of force.

❖ **Liver targeting micelles**

Polymeric micelles have advantages, like the small size and narrow size distribution, future survival in blood circulation, and solubilization of hydrophobic drugs because of these advantages, they are very useful to deliver the anticancer drug. These have the nanometric size distribution and it formed from self–assembled amphiphilic block copolymers having core–cell architecture in solution. Therapeutic agents remain during this hydrophobic core and avoid possible degradation during in vivo transportation and the hydrophilic shell of micelle maintains a hydration barrier that may effectively stabilize the drug-loaded micelles within the blood circulation. [11] Silibinin and siCol1α1 loaded Vitamin A–decorated

biocompatible micelles were developed to deliver therapeutic molecules safely and efficiently to HSCs to inhibiting fibrous collagen–I for the treatment of liver fibrosis.

❖ **Nanoshell**

It is a promising tool for liver targeting. One of the most important nanoshells is gold nanoshells. According to Liu et al, (2010), gold nanoshell showed good targeting ability to liver cancer cells, for example, BEL7404 and BEL-7402 without affecting the normal healthy liver cell-like HL-7702.

❖ **Inorganic Nanofiber**

Nanofibers are considered nearly as good carriers for drug delivery of liver diseases. Zhang et al, (2014) investigate cisplatin-loaded, multi-layered polylactide electrospun nanofiber in liver disease in mice. They evaluate the inhibitory effect of cisplatin-loaded nanofiber within the H22 cell lines. The nanofiber improved tumor cytotoxicity and prolonged drug release and forestall tumor recurrence following HCC surgery.

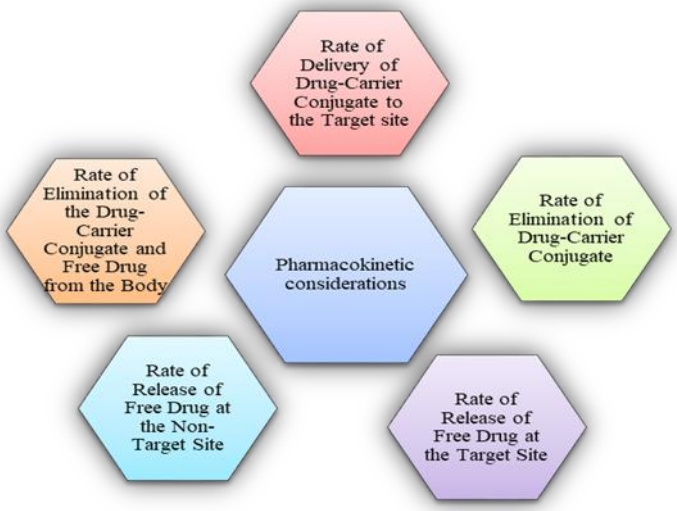
❖ **Carbon Nanotubes**

These are needle-like shape materials. That can able to carry therapeutic drugs to the cellular component.[12] CNTs are potentially considered excellent nano-vehicles for the delivery of different therapeutic agents due to their small size, high electrical potency, strong mechanical potency, and thermal conductivity. CNTs exhibit biocompatibility, low toxicity, fewer side effects, and high treatment efficacy with low drug doses in tumor-targeted liver drug delivery. Qi et al (2015) had used CNTs as a carrier to deliver the doxorubicin drug *in vivo* liver tumor model and found excellent antitumor activity in the Hep2 cell lines.

ESSENTIAL ATTRIBUTES FOR DESIGNING DELIVERY SYSTEM FOR LIVER TARGETING

Pharmacokinetic Considerations

Pharmacokinetics also plays an important role in developing novel delivery systems of herbal drugs for the liver, since the introduction of this tool enables us to quantitatively predict the disposition of drugs after modification.



Rate of Release of Free Drug (unbounded drug) at the Non-Target Site.

The discharge of drugs at the non-target site could nullify any benefits that will potentially come from delivering the drug to the target site. This is because the amount of drug reaching the non-specific sites may cause toxicity thanks to its high concentration.

Rate of Delivery of Drug -Carrier Conjugate to the target Site.

If the drug-carrier conjugate reaches the target site too slowly, the availability of free drug might never be sufficient to come back up with the concentration required to elicit the specified therapeutic effect at the positioning of action. The complete amount of drug delivered (i.e., the earth under the curve in an exceeding drug concentration versus time plot for the target site) is irrelevant if, at any time, the free-drug concentration at the target site doesn't reach its pharmacologically effective level. Delivery of the drug-carrier conjugate to the organ won't guarantee.

Rate of Elimination of Drug-Carrier Conjugate

It should be removed in a very controlled manner from the circulation. At the time of designing and development of targeted delivery systems, all the nonspecific interactions between drug-carrier conjugate and also the environment of the systemic compartment must be eliminated. The carrier should have the flexibility to limit all unwanted interactions between the drugs and therefore the physiological environment until the drug is released at the target site.

Rate of Release of Free Drug at the Target Site

The capacity of the drug delivery system selected for the discharge of free drug from the conjugate should be considered. It must be suitable for processing the whole lot of the drug-carrier conjugate arriving at the target site, doing so at a rate that also ensures drug accumulation at the target site.

Rate of Elimination of the Drug-Carrier Conjugate and Free Drug from the Body

The elimination of the entire drug-carrier system should be minimal. These systems are large to be eliminated via the kidneys. Consequently, the liver is principally chargeable for the removal of drug conjugates from the circulation. The speed of elimination of the free drug from the circulation should be rapid relative to its rate of transfer from the target site to the central compartment of the body; the drug-delivery system will achieve a decrease within the drug-associated toxicity.

Liposomes, viruses, polymers, and modified proteins all are widely used as liver-specific drug carriers and after the most recent developments of carriers to hepatic stellate cells and channel epithelial cells, all resident cells may be reached by cell-specific carriers nowadays.

The general structure of most of these different carriers is schematically outlined. [13]

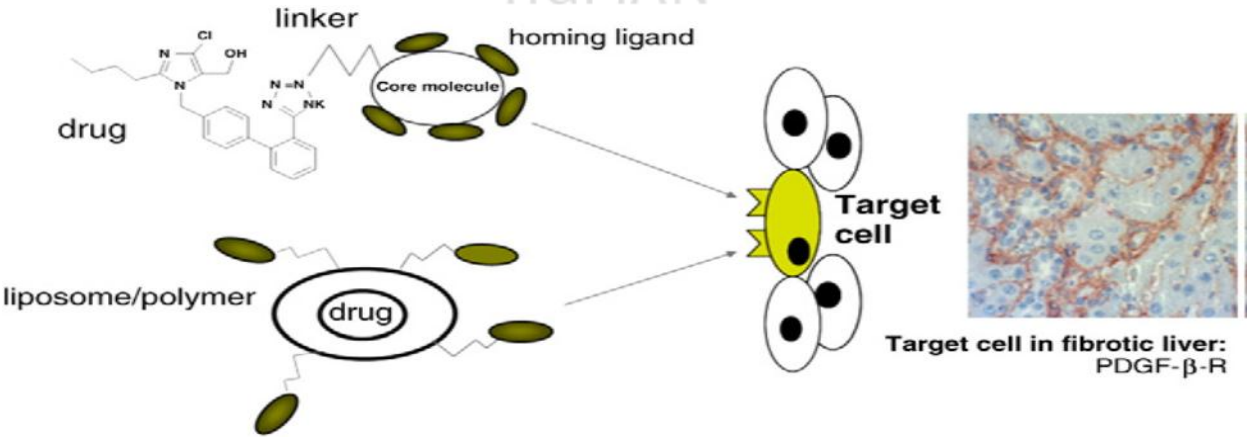


Figure No. 2: Schematic representation of the structure of carriers

The drug and therefore the homing ligand is either directly coupled to the core molecule (a polymer of protein; upper structure) or incorporated inside the core molecule (liposome, micelle; lower structure). Coupling requires the utilization of a linker molecule that's stable within the circulation but releases the drug at its target site. An example of such a target receptor during a diseased liver is provided within the right-hand picture showing the

immune histochemical staining for the Platelet-Derived Growth Factor beta-receptor in a fibrotic rat liver.

Most research in the liver targeting field has been dedicated to the delivery of genes and other gene modulating substances in particular to hepatocytes, either because the carrier was found to accumulate in this cell type (adenoviruses) or because the carriers are directed to the ASGP-receptor which was identified already in the early eighties as a useful target receptor for hepatocyte-selective carriers.

NOVEL MATERIALS USED FOR LIVER TARGETING

A) ASIALOGLYCOPROTEIN RECEPTOR (ASGP-R) TARGETING MATERIALS

This receptor is chargeable for the clearance of glycoproteins with desialylated galactose or acetylgalactosamine residues from the circulation by receptor-mediated endocytosis.

1) Galactose Ligand:

The galactosylated surface is a horny substrate for hepatocyte culture due to the precise interaction between the galactose ligand and also the asialoglycoprotein receptor on hepatocytes. The density of galactose is one amongst the important parameters for the hepatocyte attachment because it may be a major determinant of the hepatocyte attachment, morphology, and functions.

2) Lactoferrin (Lf):

Could be a mammalian cationic iron-binding glycoprotein belonging Lactoferrin (Lf), a mammalian cationic iron-binding glycoprotein belonging to the transferrin (Tf) family. Lf-R may well be a promising candidate for hepatocellular.

Carcinoma targeting thanks to its high affinity for ASGP-R, and developing a hepatic carcinoma targeting drug delivery system employing the ASGP-R targeting ability of Lf-R is extremely possible.

3) Asialofetuin (AF) Ligand:

AF is a natural ligand it could be a glycoprotein. it also contains three asparagine-linked complexes, carbohydrate chains with terminal LacNAc (N-acetyllactosamine) residues. The expressed protein displays affinity to hepatocyte ASGP-R and is endocytosed by the cells.

4) Soybean-Derived SG Ligand:

Soybean-derived SG may be a residue extracted from soybeans. Maitani et al. investigated the interaction of liposomes surface-modified with soybean derived sterol glucoside(SG-liposomes) and SG-liposomes are potentially useful drug carriers to focus on the liver, because the glucose residue may match as a sort of ligand for ASGP-R.

5) Glycyrrhetinic Acid (GA) Receptor Targeting Materials:

Glycyrrhizin (GL) and glycyrrhetinic acid (GA) are the most bioactive compounds of licorice and are widely utilized in medicine for the treatment of the many pathologies, like anti-inflammatory, anti gastric, anti-hepatitis, antiallergic, and antihepatotoxic effects.

B) MANNOSE RECEPTOR TARGETINGMATERIALS.

Mannose receptors are known to contribute to the defense reaction of mammals by endocytosis or phagocytosis of terminal mannose bearing exogenous materials. Mannose is the sugar monomer of hexose. it has several important biological roles one of the roles is the glycosylation of proteins.

A mannose 6-phosphate binding protein with a subunit and molecular size of 215, 000 has been isolated from bovine liver. The expression of mannose-6-phosphate on rat hepatic stellate cells is increased during liver fibrosis.

FORMULATION ASPECTS OF LIVER TARGETING OF MEDICATION

Normally most of the drugs achieve high hepatic concentration, still, their targeting is important because the liver is that the major organ within the body. The xenobiotics uptake, detoxification, metabolic transformation, and excretion done through a carrier-mediated mechanism. The entire liver uptake depends on hepatocytes. The drugs that enter the liver intrinsically or within the type of covalent carrier conjugates won't necessarily reach the desired cell type. If the drugs are accumulated within the liver, their continuance within the organ is influenced by the factors discussed under macrophages interaction with the delivery system, and pharmacokinetic consideration. Thus, the challenge is to get a selective accumulation of medication in one specific cell type and to sustain intracellular levels for an extended period.

There are various methods for the coupling of ligand molecules on the drug delivery system so that the drug-carrier system will be targeted to the liver cell via receptor-ligand processes.

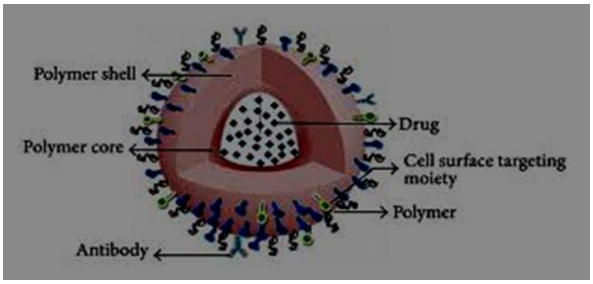


Figure No. 3: Drug delivery system encapsulating drug grafted with a targeting moiety

Different methods for coupling of ligand molecule on the drug delivery system are;

Coupling of targeting moieties –

On preformed Nanocarriers,

By the post-insertion method,

By the Avidin /Biotin complex,

Before Nanocarriers formulation.

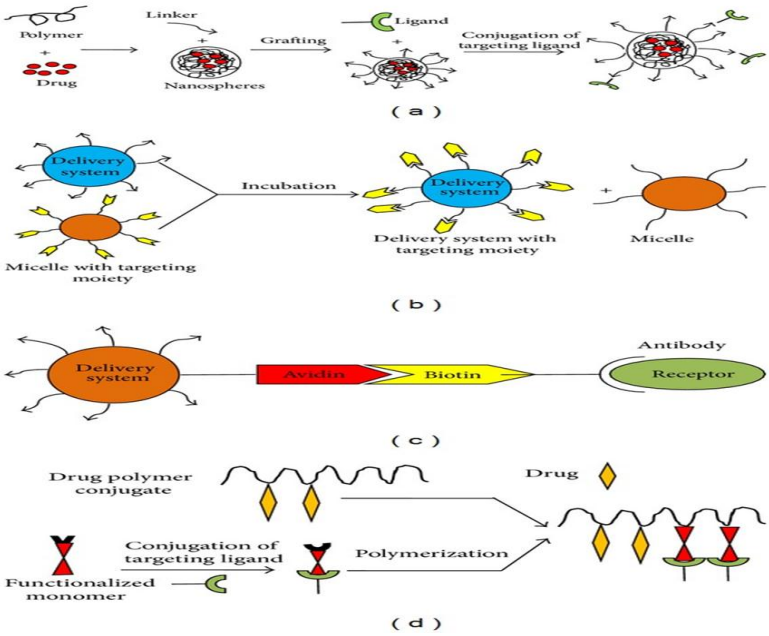


Figure No. 4: Different methods for coupling of ligand molecule on drug delivery system

CONCLUSION

The pathogenesis of liver diseases involves a range of cells which makes the delivery of drugs complicated. The foremost important aspect to boost the treatment via hepatoprotective drugs is the planning and synthesis of appropriate polymeric material to focus on specific cells of the liver. Ingenious studies are required in coupling and selection of targeting moiety so they may be translated from the bench research to the bedside. Selection of ligands and their coupling to drug/polymer which might potentially target parenchymal/non-parenchymal liver cells. The pharmacokinetic behavior and physicochemical factors related to delivery systems are considered to be primarily to blame for the improved targeting and therapeutic effectiveness; therefore, handling these factors during formulation development may lead to brighter treatments for acute and/or chronic liver diseases. Each disease has its target cell, nearly all resident hepatic cells may be reached nowadays using different drug delivery systems. To stop that drug targeting is viewed upon as posh thanks to delivering a drug to an organ that takes up most drugs anyhow, it's now essential to demonstrate the advantages of cell-selective drugs in vivo relative to untargeted drugs. The incidence of many liver diseases is increasing, in contrast to most other diseases within the world. [14] Therefore the incontrovertible fact that this organ is quickly accessible by all drugs, no pharmacotherapy is on the market for many liver diseases. Therefore we want a replacement strategy to treat hepatic diseases and cell-specific delivery of medication may represent such a unique strategy.

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