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Novel Drug Formulation for the Treatment of Hepatic Cancer- A Review

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Abstract

For metabolic transformation, uptake, detoxification, and excretion liver is the primary organ that is highly equipped. Thus, the liver requires targeting by means like a carrier-mediated mechanism to take xenobiotics into the bile, though high hepatic concentration is achieved by most of the drugs. Thus resulting in high first-pass metabolism displayed by the drugs and thus resulting in rapid clearance of the drugs. Uptake of particulate materials is highly contributed by the kupffer cells largely. However, drug uptake by the liver is highly dependent on hepatocytes. In drug delivery, tissue engineering and regenerative medicines which are various biomedical applications construction of nanoscale based bioactive materials is a desirable approach of self-assembly. By using a targeting moiety, we can decrease the side effects of the drug and increases the therapeutic effect of the drug. Lipoproteins are potential drug carrier to target the organs. Lipoproteins consist of cholesterol, polar lipid core surrounding phospholipid monolayer and apoproteins are embedded in it, and these lipoproteins are spherical. The core is a polar lipid in nature so that highly hydrophobic drugs are easily incorporated into the core. Lipoproteins are completely non-immunogenic, biodegradable nature. The present review should be regularly inspected to beat into the global market at an affordable price as well, particularly the vehicles which are proven to be efficacious in drug delivery systems used to treat liver diseases like cancer.

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INTRODUCTION

Novel Strategies and significance of hepatic delivery of drugs

For metabolic transformation, uptake, detoxification, and excretion liver is a considerably major organ that is highly equipped. Thus, the liver requires targeting by means like a carrier-mediated mechanism to take xenobiotics into the bile though high hepatic concentration is achieved by most of the drugs. Thus resulting in high first-pass metabolism displayed by the drugs and thus resulting in rapid clearance of the drugs. Uptake of particulate materials is highly contributed by the kupffer cells largely. However, drug uptake by the liver is highly dependent on hepatocytes, which makes a clear note that not all the drugs that enter the liver will require cell type in either of their carrier covalent form or as a drug as such.

The residence time of drug, if they are accumulated in the liver, depends on considerations of pharmacokinetics and macrophages interactions in the delivery system. Therefore, the main aim is to target the selective drug accumulation for the drug to be effective for more extended periods (Wisse *et al.*,

2008; Ogawara *et al.*, 1999).

Vitamin A is usually present on the surface of the colloidal delivery system. During the process of liver fibrosis, during the process of coupling with these cells, the stellate cell plays a significant active role. To target endothelial cells and Kupffer cells is served by scavenging receptors.

The criteria enlisted below are to be met for ensuring such interactions that are desired for anatomical locations in the liver (Allen *et al.*, 1991; Wu *et al.*, 2002):

1. The drug must cross anatomical barriers like intestine and stomach.
2. Receptors like glycoprotein present on the liver cells should be able to recognize selectively by the drug.
3. A ligand that has been produced exogenously should effectively compete with the ligand that has been produced endogenously.
4. In both the scenarios of *in vitro and in vivo*, the significant characteristics required are biocompatibility, nontoxicity, biodegradability and physio-chemical stability for a fabricated delivery system.
5. The capillary distribution must be smooth sinusoid.
6. For ensuring that the hepatic cells would release only the therapeutic amount of the drug, the hepatic cell drug release must be controllable.
7. Drug distribution should not affect drug release.
8. Minimal drug leakage should be established by the drug while passing through the intestine, stomach and other parts of the body.
9. No modulation in the disease state should be seen by the carrier used.
10. There should not be any signs of toxicity by the carrier, and it should be easily eliminated.
11. Finally, the formulation of the drug delivery system should be cost-effective, reproducible, and straightforward.

Controlled drug delivery vehicles

To overcome the difficulties faced by the drug delivery systems in treating disease related to the liver like liver cancers by their first-pass metabolism, many kinds of drug delivery vehicles have been recently developed. Here we discuss the various techniques employed for different drug delivery techniques (Wolfrum *et al.*, 2007).

Self-assembly as a drug carrier

In multiple geometries organization of molecules into ordered structures is self-assembly with a free energy-driven process for molecules.

In drug delivery, tissue engineering and regenerative medicine which are various biomedical applications construction of nanoscale based bioactive materials is a desirable approach of selfassembly.

In self-assemblies, the molecular structures can be turned through environmental conditions like solvents, temperature, pH and ionic strength, molecular chemistry (Akinc *et al.*, 2010; Bijsterbosch, 2000).

Nanocarriers of Protein-based

Serum albumin, HAS(human serum), bovine serum albumin, BSA(bovine serum), ovalbumin (egg white) are the different sources for getting albumin as a protein which also includes grains, milk and soybeans. (Wasan *et al.*, 2008; Kunjachan *et al.*, 2012)

There are various advantages which include long half-life in the circulating plasma, high binding capacity, non-immunogenic, biodegradable, non-toxic properties in albumin-based nanocarriers.

The availability of amino groups and carboxylic groups on the surface of albumin nanoparticles is required for binding and the surface modification and targeting ligands (Wáng *et al.*, 2015; Fiume *et al.*, 1995).

Organic nanocarriers

Polymeric nanoparticles possess nanoscale dimensions which are usually colloidal, biodegradable, biocompatible and solid.

To build a desired nanoparticle and for nanomedicines applications, polymeric nanoparticles are simplest soft materials, for surface modification to improve drug loading efficacy, biodistribution, therapeutic efficacy and pharmacokinetic control nanoparticles are used (Beljaars *et al.*, 2002; Meijer *et al.*, 1992; Rensen *et al.*, 2001b).

Supramolecules as a delivery vehicle

Due to reversible and weak noncovalent interactions, such as metal coordination, hydrogen bonding, hydrophilic attractions, $\pi-\pi$ and electrostatic interactions, Vander Waals forces molecular entities are stabilized and it leads to an assembling of supramolecules.

Table 1: Receptors present onvarious hepatic cell and may be used for drug targeting

Hepatocytes	Kupffer cells	Endothelial cell	Hepatic stellate cells
Asialoglycoprotein receptor (ASGP-R)	Mannose/N-acetyl glucose amine R	Mannose/N-acetyl glucose amine R	M6P/IGF II R
HDL-R	Galactose particle R	Scavenger R (Class A1 and A11)	α2 macroglobulin R
LDL-R	Galactose specific R	Fc R immune complexes	Ferritin R
IgA-R	Fc R (immune complexes, opsonized material)	Matrix compound (hyaluronan fibronectin, denatured collagen PIIINP)	Uroplasminogen R
Scavenger R (Class BI)	Scavenger R (Class AI, BI, BII, MARCO CD36 and macrosialin)	-	Thrombin R
Transferrin R	LDL R matrix compounds (fibronectin)	-	RBP R matrix compounds (intregrin, collagen type VI, fibronectin CD44)
Insulin R	Complement R (C3b and C1q) LPS R α2 macroglobulin R	-	

These are used in drug delivery designs. The supramolecular systems provide the necessary targeted delivery for the bioactive and therapeutic agents (Unezaki *et al.*, 1994; Lai *et al.*, 2018).

Micelles as a drug carrier

In an aqueous solution, amphiphilic block copolymers are self-assembled it leads to the formation of global colloidal nanoscale systems or spherical micelles, this results in a hydrophilic shell and a hydrophobic core. Under certain temperatures and concentrations (critical micelle concentration; CMC), spontaneously amphiphilic colloidal groups are formed. For an appropriate administration by IV, the hydrophobic drugs are reserved by hydrophobic cores, and these hydrophobic cores are stabilized by hydrophilic shell renders both hydrophobic drugs and polymer are water-soluble. Drugs get incorporated into polymeric micelle by chemical, physical and electrostatic interactions (Allen *et al.*, 1989).

Inorganic nanocarriers

Due to various properties shown by inorganic nanocarriers like large surface area, controlled drug release, better bioavailability, lower toxic effects, lower side effects, better drug loading capacity and compatibility with various organic solvents unlike polymer-based nanoparticles made it a bigger platform for investigation in recent years. The most commonly used particles in cancer treatment include mesoporous silica, quantum dots, carbon tubes, magnetic nanoparticles and layered double hydroxides (Dasgupta and Bachhawat, 1985). Some of the proven powerful imaging probes included quantitative imaging, multiplexed imaging and diagnostic quantum dots (Spanjer and Scherphof, 1983).

Topics to discuss

The present review is aimed to deal with various novel drug formulation techniques and their multiple aspects for the management of hepatic cancer, as enlisted below:

1. The Liver cancer delivering strategies.
2. The liver cancer-targeting drug delivery systems application and constructions based on core-shell gold nanocages.
3. Indocyanine green can be used as novel liver-specific fluorescent, which is an anti-cancer drug delivery system.

MATERIALS AND STRATEGIES USED IN CANCER THERAPY

Cancerous Liver Cells Over Expressing The Targeting Carboxyl Esterases (CES)

The CES-1 or the CES-2 present in the liver activates the drug present in the liver. When the CES-1(Carboxyl esterase-1) and CES-2(Carboxyl esterase-2) are overexpressed, the derivative of the drug is activated.

Hydrolysis of various esters and carbamates is caused by carboxyl esterses which are also called serine esterses. Some anti-cancer drugs are known to target the carbamate prodrugs in case of liver cancer. 5-FU, doxazolidine and camptothecin are some of the examples of carbamate prodrugs.

Tethering bile acids

By the process called sodium-independent transport carrier presented by the hepatoma cells, the bile acids also target liver cancer. In both *in-vivo* and *in-vitro* the investigations were run on synthesized bile acid-platinum conjugates cytotoxicity.

The conjugate Bamet-UD2 exhibited a similar ability to that of cisplatin by enhanced hepatocyte uptake by showing prolonged survival time and by the process of inhibited tumour growth.

Treating liver cancer with glass beads

Tiny radioactive glass beads are recently evolved and used to treat liver cancer. These radioactive glass beads are sent into the liver by injecting them into the large artery that supplies blood to the liver. Thus, these radioactive glass beads deliver their radiation on the malignant liver cells with blood as medium (Shimizu *et al.*, 1997).

Targeting based on HDL (High-Density Lipoprotein)

The increase in beneficial therapeutic effect and a decrease in undesirable side effects by the drug can be achieved by using targeting moiety. Lipoproteins are potential drug carrier to target the organs. The lipoproteins are spherical—these consist of polar lipids and cholesterol and apoproteins embedded in them. High hydrophobic drugs can easily incorporate into the core as it is of polar lipid nature.

The RES system cannot recognize Lipoproteins. They are completely biodegradable and non-immunogenic. The important medium of lipoprotein that transports in cholesterol is the HDL (high-density lipoprotein) (Maitani *et al.*, 2001).

Surface modified liposome

Both hydrophilic and lipophilic drugs are present in the novel drug delivery system, so the drugs can easily encapsulate into it. The drug can easily target the desired site of the body or the organ due to surface modifications of the liposomes.mLiposomes are mostly accumulated in the liver in non-parenchymal cells, because when liposomes are administered intravenously in the liver are part of RES by RES. Kupffer cells.

Galactose moiety is the ligands that are present on the surface of the liposomes. By the process of endocytosis, they are incorporated into the liposomes which are used in recognizing the hepatocyte ASGP receptors.

Lactosylceramide, synthetic glycolipids or asialofetuin are used to modify the liposomes are terminated by galactose. Like liposome having sterylglucoside accumulated in the liver, particularly in hepatocytes (Drager *et al.*, 2018).

Chylomicron emulsion

Lipoproteins are also called spherical and natural macromolecular emulsion particles. These are involved in cholesterol and intercellular lipid transport in the circulation. Blood absorbs the dietary lipids through the intestine membrane into the bloodstream and is packed into chylomicrons, and these are also called triglycerides-rich lipoproteins emulsion.

The core triglycerides of the chylomicron can be hydrolyzed by a lipoprotein enzyme called lipase in blood circulation. Their receptors anchor many different apolipoproteins on the surface of the chylomicron, and these chylomicrons are taken up by the liver parenchymal cells because it is completely modified (Hara *et al.*, 1997).

Core-Shell Gold Nanocages Based Construction And Application Of A Liver Cancer-Targeting

Due to the porous walls present on the gold nanocages, it becomes nanoscale carriers. It is possible to tune localized surface plasmon (LSPR) properties by near-infrared region (NIR) of light in peaks. On the surface of Au with Au-S bond, many kinds of ligands and molecules are modified. The Raman electrochemical biosensor is used to study the damaging effects on DNA by anti-cancer drug doxorubicin (DOX).

The P (NIPAM-co-Am) (PM) and N-isopropyl acrylamide (NIPAM) copolymers are reported to have thermosensitive and biodegradable properties, To know the drug control release, and the thermosensitive PM can be used as aids (Valicherla *et al.*, 2016).

For obtaining a lower critical solution temperature (LCST), acrylamide copolymerization should be done. Hyaluronidase(HAse) is an enzyme existing at

both the external and internal regions of the tumour cells can be used to degrade the natural, non-toxic and biodegradable polymer Hyaluronan (HA). The CD44 receptors on the cancer cells are overexpressed, and they promote the HA-nanoparticles of the cancer cells to enable HAase bound HA degradation.

In response to the HAase present in the intracellular environment of the capping agent, the controllers used include the tumour cells and the HA cells.

Thus, materials like copolymer PM, HA and AuNCs are appropriately required in making up of novel drug delivery systems (Kagawa, 2017; Rensen *et al.*, 1995, 2001a) (Table 1).

Indocyanine Green Used Novel Liver-Specific Fluorescent Anti-Cancer Drug Delivery System

In Vitro Effects Of Anti-Cancer ICG-Conjugated Drug

The anti-cancer activity containing ICG-conjugated anti-cancer drug is evaluated. The assay is performed on MTT cells proliferation of HCC. In in vitro, HepG2 cells are suppressed by the action of anti-cancer agents such as Gem and ICG-Gem, and at lower concentration superior cytotoxic effect in HuH-7 is demonstrated by ICG-Gem. In comparison with HepG2, the ICG-Gem cells are known to better known to accumulate in HuH-7 cells with their consistent results. Gem is also reported to be more toxic in comparison with HUVEC than ICG-Gem. ICG-Dox is known to relatively impair the cytotoxic effect.

In Vivo Effect Of ICG-Gemcitabine Complex

24h analysis the fluorescent distribution after injection of ICG-Gem through the tail vein of tumour-bearing nude mice. The ICG-Gem accumulated in HCC cell (HuH-7) tumour xenograft but not in the colon cancer cell (HCT116). ICG-Gem is accumulated in the liver and excreted through stools and bile ducts, not in urine, but the urine excretes g6y itself.

Thus, ICG-Gem may be considered as difficulty in serving as a selective HCC cell administrating agent. ICG-Gem may face difficulty to serve as a systemic chemotherapeutic agent. In the subcutaneous tumour xenograft region, ICG-Gem is directly injected as a model of HAIC (Senapati *et al.*, 2018).

After longer than one week in subcutaneous tumour xenograft, the accumulated ICG-Gem is detected. It was also revealed from the study that compared to healthy cells, ICG cells are less toxic (Mishra *et al.*, 2013; Inagaki *et al.*, 2019; Mengfei *et al.*, 2018).

CONCLUSION

It could be concluded from the review that by improving the polymeric materials and synthesis of hepatoprotective drugs, the target-specific cells of the liver can be reached. For the selection of targeting moiety and for coupling ingenious studies were however required. The primary considerations for improving therapeutic effectiveness and targeting depend on physiological factors and pharmacokinetic behaviour of the drug delivery system. It was proven from previous studies that novel HCC-specific fluorescent DD Scan is contributed by ICG conjugation and ICG-Gem can be considered an HCC-specific promising agent. For improved theranostic applications. Thus, for both liver cancer treatment and diagnosis, the DOX/AuNCs-PM-HA can be considered as a promising system.

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Conflict of Interest

The authors declare that there is no conflict of interests.

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