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NANOFORMULATION APPROACHES FOR LIVER TARGETED DRUG DELIVERY- A REVIEW

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ABSTRACT

Many serious liver diseases affecting millions of people in world cannot be treated which requires some novel therapeutic strategies. Drug delivery to liver is one of the challenging research areas in pharmaceutical sciences. Some physiological barriers like opsonization, mechanical entrapment by pulmonary vascular bed, uptake by recticulo endothelial system represents an indomitable obstacle for a large number of proteins and drugs, including antibiotics, antiviral agents and anticancer agents to target liver disorders. So different techniques have been adopted to improve the delivery of different drugs to liver and hepatocytes which contains 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 targeting strategies of liver and different nano formulation approaches towards the liver targeted drug delivery.

INTRODUCTION

Nanotechnology-based techniques have been used previously to enhance the solubility and bioavailability of many potential phytochemicals and to provide them a robust strength against physical, chemical, and environmental degradation. According to National Nanotechnology Initiative , nanotechnology has been broadly described as the science and technology involved in the design, synthesis, characterization, and application of materials and devices with at least one of the dimensions on the nanoscale (usually in the range of 1–100 nm)[1]. This approach offers several potential advantages to medical applications including the early detection of cancers and cancer treatment, passive and active disease targeting, increased biocompatibility, and multi functionality encompassing both imaging and therapeutic capabilities, allowing for simultaneous disease treatment and monitoring [2]. The application of nanotechnology in medical sciences is changing the landscape of drug delivery and tissue engineering industry as a whole [3,4.] Nanostructured biomaterials, featuring a nanoscale morphology and size, exhibit a wide range of advantages over the conventional biomaterials, such as high bioavailability, improved cellular interaction, and specific designed functions[5]. It offers a promising solution to many difficulties in drug delivery

and tissue engineering, for example, a nano-sized drug vehicle can make significant progress in the delivery of conventionally undeliverable molecules, such as compounds with low water solubility and genetic biomolecules [4,6]. The newer formulation design approaches for bioavailability enhancement includes incorporation of the active component into inert lipid vehicles [7] such as oils, surfactant dispersion, self-emulsifying formulation, emulsions, micro or Nano emulsions and liposomes. The liver is an important organ for the maintenance of metabolic functions and detoxification of endogenous and exogenous challenges like drugs, viral infections, xenobiotics 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 [8-10]. Nano carrier drug delivery systems, which contains therapeutic drugs, peptides, proteins or nucleic acids in association with a carrier, should have size range of 10-200 nm.

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 [11]. In following sections, the physiological and anatomical barriers to hepatic accumulation can be overcome through passive accumulation of nano carrier therapeutics and active targeting by surface modifications of nanoparticles with specific ligands such as carbohydrates, peptides, proteins and antibodies.

DRUG TARGETING [12]

Drug targeting is defined as the ability of a drug to accumulate in the target organ or tissue quantitatively and selectively, independent of the site and methods of administration. Ideally, under such conditions, the local concentration of the drug at the disease sites 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 advantages of drug targeting are that the drug administration protocols can be simplified, drug quantity required to achieve a therapeutic effect can be reduced, the cost of therapy can be reduced and drug concentration at the required sites can be increased tremendously. Three components required for drug targeting are: 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 identification 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, for every organ or tissue, certain compounds (antigens) can be found that are specific only for the organ of interest. For achieving successful targeting, another compound can be used as a transporting unit, which can make specific interaction with the specific target component. Based on this principle, numerous systems for drug targeting have been formulated which are capable of the delivery of pharmaceuticals to variety of tissues and organs.

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 reticulo endothelium or active targeting based on recognition between hepatic receptor and ligand-bearing particulates [13].

Passive targeting: Passive targeting refers to transportation of nanoparticles 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. [14] Size properties

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

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.

Drug targeting to Hepatic stellate cells (HSCs): The five main strategic tools make the use of properties 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 up regulated 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 [15].

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-vinylbenzylO-β-Dgalactopyranosyl-[1- 4]-D-glucosamine (PVLA) for target in to hepatocytes. In polymeric systems, the most commonly used technique is through coupling of lactobionic acid or lactose to the nano carrier through carbodiimide chemistry, with the final product retaining functional galactose moieties. For targeting of polymeric nanoparticle to liver,various ligands such as folic acid , asialoglycoproteins, galactosyl residues and glycyrrhizin derivatives, have been introduced into drug carriers. Albumin nanoparticles with surface modification by galactose residues have been formulated to achieve the effective targeted delivery of Oridonin into liver cancer cells [16]. Conjugating glycyrrhizin (GL) to the surface of chitosan nanoparticles (CS-NPs) by an ionic gelation process [17] resulted in a targeted drug delivery system to the liver through a specific interaction between glycyrrhizin and hepatocytes.

DIFFERENT NANO FORMULATION APPROACHES TO ACHIEVE HEPATO TARGET DELIVERY

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 [18]. 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 [19]. Nanoparticles vary in size from 10 to 1000 nm. In the preparation of Nanoparticles, drug is dissolved, encapsulated entrapped or attached to polymeric matrix and depending upon the method of preparation, nanoparticles, nano-spheres or nanocapsules can be obtained.

Nanoemulsion and microemulsion systems: Nanoemulsions are defined as thermodynamically/ thermokinetically stable isotropic system, containing transparent dispersions of oil and water stabilized by an interfacial film of surfactant molecule. Nanoemulsion droplets usually have the droplet size between 10 and 100 nm [20]. Microemulsions are thermodynamically stable systems, which are similar to nanoemulsions in appearance and form spontaneously. Microemulsions are mainly differentiated from nanoemulsions by their spontaneous formation, which requires higher concentration of surfactants than nanoemulsions [21]. Maximum size of nanoemulsion droplet is 150nm.

The nanosized droplet in nanoemulsion leads to increase in interfacial area influencing the transport properties of the drug [22]. These systems have been reported to make the pharmacokinetic profiles and bioavailability of drugs more reproducible [23-25].

Solid lipid nanoparticles (SLNs): Solid lipid nanoparticles offer the alternative mechanism for drug delivery in comparison to other colloidal systems such as emulsions, liposomes, and polymeric nanoparticles. They combine advantages of other colloidal systems while minimizing their drawbacks [26]. SLNs are easy to be produced on a large scale by simple methods, offering better physicochemical stability and protection against degradation of labile drugs [27-29]. They are produced from lipids that are solid at room temperature. The solid lipid is melted and the drug is incorporated into it. The whole system is stabilized by the addition of a suitable surfactant [30]. The matrix of the lipid particle is made in solid which can easily protect the drug molecules against chemical degradation. The addition of lipid/oil to an o/w emulsion containing a solid lipid, or mixture of solid lipids, results in the formation of SLN. Because of their small size (50–1000 nm) and biocompatibility, SLNs can be used in the pharmaceutical field for various routes of administration, such as oral, parenteral, and percutaneous routes.

Nanosuspension: Reducing the size of particles helps to overcome the stability problems associated with suspensions. Silymarin nanosuspensions were prepared by microemulsion dilution technique. Drug solution is made by dissolving in butyl lactate and then this mixture was dispersed in a mixture of aqueous surfactant solution (the mass ratio of castor oil polyoxyethylene ether (EL-40): ethanol that is 3:1) by gentle stirring. Results indicated that silymarin nanosuspensions were successfully prepared in the size range of 31–326 nm with enhanced stability [31].

Liposomes: Liposomes are spherical, self-enclosed structures with a lipid bilayer (ranging from some nanometers to several micrometers) that possesses a unique amphiphilic character [32]. This form overcomes the difficulties associated with pharmacokinetic parameters of silymarin and helps in targeting the drug to hepatocytes. Liposomal systems have been found to be useful and effective in targeting to liver cells.

Newer formulation aspects which could be adopted for successful formulation and targeting hepatocytes

Emulsomes: Emulsomes has the combination of the advantages and features of liposomes and emulsions. They protect the drug from harsh gastric environment of GIT and can be used for targeting to specific tissues [33]. The emulsomes are designed to act as a carrier for drugs which have poor water solubility. Its internal core is made up of fats and triglycerides, which are stabilized in the form of o/w emulsion by addition of high concentration of lecithin .Due to its solidified or semi-solidified internal oily core, it provides better opportunity to load lipophilic drugs in high concentrations and to provide a controlled release delivery of the drug. They also have the ability to encapsulate water soluble medicaments in an aqueous compartment of surrounding phospholipid layers [34]. Emulsomes reduce the toxicity issues by providing a prolonged action at lower doses of the drug at the desired target site [35]. This is a new drug delivery system which has ability to overcome solubility and bioavailability related problems .With silymarin, emulsomes may be used to enhance

the oral drug delivery and targeting of silymarin to liver cells.

Polymeric nanoparticles (PNPs): Polymeric nanoparticles are solids having spherical structures of about 10–1000 nm in size, prepared from biodegradable and biocompatible polymers to provide controlled release of the drug at the desired target site [36-39]. They can appear either as nanocapsules and/or nanospheres. One of the most important barriers to nanoparticles-based controlled drug delivery is to target hydrophobic drug to desired site, as the body recognizes them as foreign particles. The reticulo-endothelial system (RES) eliminates these from the blood stream and takes them up in the liver or the spleen [40]. PNPs can be successfully delivered to cancer cells, and this can be achieved either by active or passive targeting [41]. Development of PNPs of Silymarin will overcome difficulties encountered while targeting them to hepatocytes.

Nanocrystals: Nanocrystals offer solubility and bioavailability enhancement to poorly soluble drug coupled with many other advantages such as providing sustained release action, dose reduction, targeting to various tissues etc. As the size of the silymarin particles are reduced to nanoscale in nanocrystals, the surface area is increased leading to enhanced solubility and hence bioavailability. Nanocrystals have a solid, crystalline drug core in nanometer size range and an outer layer of stabilizer .Since, nanocrystals are often prepared in aqueous solution or non-aqueous solvent medium, the word nanosuspension is also used to refer to nanocrystals meaning a sub-micron colloidal dispersion of pure drug particles, which are stabilized by surfactants, polymers, or both [42].

Cerasomes and mesoporous silica nanoparticles (MSNs) Ceramide is a lipid, which is naturally present in the plasma membrane of cells and controls the cell functions. Recently developed novel class of ceramic nanoparticles comprises of liposomal organic–inorganic hybrid nanoparticles known as cerasomes [43-45]. They have a liposomal bilayer structure and a siloxane network on their spherical external surface and these may provide alternative therapeutic system to existing common chemotherapeutics. Cerasomes have different characteristics and potential applications that are same as that of liposomes. In addition, the siloxane network present on cerasomes may be exploited for surface functionalization purposes. Presence of siloxane network on the surface adds rigidity and thus overcomes the inherent morphological instability of liposomes [46], which is a serious problem in practical applications [47,48]. The external surface of cerasomes can be modified in such a way that the vesicles do not target the lipid bilayer but instead it targets the desired specific cells. After the targeting of vehicle in the cytoplasm, it is essential to have effective control over the release of drug molecules, which could result in effective pharmacological effects. Recent developments in MSNs have brought new possibilities to this burgeoning area of research. MSNs contain several mesopores, which are arranged in a 2D network of a honeycomb-like porous structure. Some studies indicated that MSNs exhibit superior biocompatibility at therapeutic concentrations in comparison with other amorphous silica materials [49,50] The ability of MSNs in selectively functionalizing the external particle and/or the interior nanochannel surface of MSNs is beneficial in achieving this goal [51,52]. The pores present in MSNs can be encapsulated with hydrophobic molecules such as silymarin. The design of these particles assists researchers to target such molecules to hepatic cells to treat various liver diseases including hepatocellular carcinoma.

Carbon nanotubes: Nanotubes are members of the fullerene structural family which are having hollow structure with the walls formed by one-atom-thick sheets of carbon, commonly known as Graphene. The sheets of carbon are rolled at specific and discrete (chiral) angles, which are helpful in evaluating the properties of nanotubes. Their design is simple which offer several intriguing and advantageous properties associated with these nanotubes. Various studies have shown that chemically functionalizing single walled nanotubes (SWNTs) allow them to become soluble without critically compromising their inherent properties.

Dendrimers: Dendrimers have been investigated as potential drug carriers, which are composed of polymeric complexes that comprise of a series of well-defined branches. The size of an inner core of dendrimers varies from 1 to 10 nm [53, 54]. Dendrimers have been functionalized using various groups such as carbohydrates, peptides, and silicon to form glycol dendrimers, peptide dendrimers, and silicon-based dendrimers, respectively. These carriers (dendrimers) have been explored for the encapsulation of poorly soluble compounds and for the targeting of several anticancer drugs. The physicochemical properties of dendrimers are helpful in making these macromolecules appropriate candidates for evaluation as drug delivery vehicles. These advantages of dendrimers could be used for bioavailability enhancement of silymarin with a targeting approach.

CONCLUSION

A thorough understanding of the anatomy, physiological function and pathological condition 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. Carriers have to be highly optimized in order to fulfill specific needs such as cellular targeting, high loading capacity, and protection from nuclease degradation, nanosize and narrow size distribution.Future research work should be aimed at the the synthesis of polymeric carriers with full biodegradability, and flexibility in adjusting the hydrophobic or hydrophilic and functional block compositions to impart the self-assembly process and allow the incorporation of targeting ligands for the specific delivery of therapeutic agents.

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