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Review Article

Vesicular drug delivery system used for liver diseases

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ABSTRACT

Liver has an essential role in the regulation of physiological process. It is involved in several vital functions such as storage, secretion, metabolism and detoxification of a variety of drugs. Liver diseases are mainly caused by either toxic chemicals (certain antibiotics, peroxides oil, aflatoxin, carbon tetrachloride chlorinated hydrocarbons etc), excess consumption of alcohol. The application of vesicular system in drug delivery has changed the definitions of diagnosis and treatment in different aspects of biomedical field. The vesicular system as liposomes, niosomes, sphinosomes, transferosomes and pharmacosomes are used to improve the therapeutic index of both existing and new drug molecules by encapsulating an active medicament inside vesicular structure in one such system. It prolongs the existence of the drug in systemic circulation and finally reduces the toxicity. In this review we really focused on different aspects of vesicular system in used in treatment of liver disease.

Kew words: Vesicular system, Liver diseases

INTRODUCTION

Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as required to safely achieving its desired therapeutic effect [1]. In the past few decades, considerable attention has been focused on the development of new drug delivery system (NDDS). The NDDS have to ideally fulfil two prerequisites. Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, it should channel the active entity to the site of action [2,3]. The novel drug delivery system is the most suitable and approachable in developing the delivery system which improves the therapeutic efficacy of new as well as pre-existing drugs thus provides controlled and sustained drug delivery to the specific site and meets the real and appropriate drug demand of the [4,5]. Novel vesicular drug delivery systems aim to deliver the drug at a rate directed by need of body during the period of treatment, and channel the active entity to the site of action. Biologic origin of these vesicles was first reported in 1965 by Bingham and has been given the name Bingham bodies [6, 7]. Targeted drug delivery is a method of delivering the therapeutic agent to the tissues of interest and increase the concentration of the drug at targeted site in the body while reducing the relative concentration of therapeutic agent in remaining tissues which improves the therapeutic efficacy and reduces the side effects [8, 9, 10]. The targeted drug delivery system was developed by Paul Ehrlich, in 1909, which delivered the therapeutic agent directly to diseased cells [11] Vesicular drug delivery reduces the cost of therapy by improved bioavailability of medication, mainly in case of poorly soluble drugs. They can incorporate both by hydrophilic and liophilic drugs. [8, 9, 11].They can incorporate both by hydrophilic and liophilic drugs. Different novel approaches used for delivering the drugs by vesicular system include liposomes, niosomes, sphinosomes, transferosomes and pharmacosomes, Emulsomes, Enzymosomes Ethosomes, Sphingosomes, Virosomes, Niosomes, Bilosomes, Aquasomes [12].Application of vesicular system as a device of targeting therapy in liver diseases is still in a period of preclinical examination. Maximum findings are from experiments with animal models and only a few clinical investigations have been reported. [13].The liver is the largest glandular organ in the body, and it has large number of functions than any other human organ. A person's entire blood supply passes through the liver several times a day. The Liver has a pivotal role in human metabolism. Liver produces and secretes bile, it also produces prothrombin and

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fibrinogen, both blood- clotting factors, and heparin, a mucopolysaccharide sulphuric acid ester that helps keep blood from clotting within the circulatory system [14]. Liver diseases have become one of the major causes of morbidity and mortality in man and animals all over globe and hepatotoxicity due to drugs appears to be the most common contributing factor. About 20,000 deaths found every year due to liver disorders [15].

VESICULAR DRUG DELIVERY SYSTEM

Novel vesicular drug delivery systems aim to deliver the drug at a rate directed by need of body through the stage of treatment, and channel the active entity to the site of action [7]. The vesicular systems are very ordered assemblies of one or some concentric lipid bilayer formed, when certain amphiphilic building blocks are confront with water. Vesicles can be formed from a diverse range of amphiphilic building blocks. Biologic source of these vesicles was first reported in 1965 by Bingham, and was given the name Bingham bodies [3]. Vesicles as a carrier system have become the vehicle of option in drug delivery and lipid vesicles were found to be of value in immunology, membrane biology and diagnostic technique and mainly recently in genetic engineering. Vesicular delivery system provides an capable technique for delivery to the site of infection, leading to decrease of drug toxicity with no adverse effects. Vesicular drug deliveries reduce the cost of therapy by enhanced bioavailability of medication, mainly in case of poorly soluble drugs. They can incorporate both by hydrophilic and liophilic drugs. Different novel approaches used for delivering the drugs by vesicular system include liposomes, Niosomes, Sphinosomes, Transferosomes and Pharmacosomes [8, 9].

Type's vesicular drug delivery system

The targeted vesicles are classified on the basis of their composition [16].

a. Lipoidal biocarriers

1. Liposomes
2. Emulsomes
3. Enzymosomes
4. Ethosomes
5. Sphingosomes
6. Transferosomes
7. Pharmacosomes

b. Non-lipoidal biocarriers

1 Niosomes
2. Bilosomes
3. Aquasomes

Liposomes: The name liposome is derived from two Greek words: 'Lipos' meaning fat and 'Soma' meaning body. Structurally, liposomes are concentric bleeder vesicles in which an aqueous [17]. Liposomes were first described by British haematologist Dr Alec D Bangham FRS in 1961 (published 1964), [8,9] Liposomes are bilayered structures composed of phospholipids and cholesterol that are used for the administration of nutrients and drugs [18]. Liposomes consist of one or more concentric lipid bilayers, which enclose an inner aqueous volume(s). For drug delivery applications liposomes are usually unilamellar and range in diameter from about 50 – 150 nm. Larger liposomes are rapidly removed from the blood circulation [19].They have lipid bilayer structures, which is present with an aqueous volume wholly enclosed by a membrane, composed of lipid molecules in such a way that both hydrophilic and lipophilic drugs can be successfully entrapped [20,21]. The lipophilic drugs get entrapped within bilayer membrane whereas hydrophilic drugs get entrapped in the central aqueous core of the vesicles [20].Liposomes can be used for both oral as well as topical drug targeting [22].

Advantages of liposomes [23, 24, 25]

Advantages of liposome are as follows:

- Provides selective passive targeting to tumour tissues (Liposomal doxorubicin).
- Increased efficacy and therapeutic index.
- Increased stability via encapsulation.
- Reduction in toxicity of the encapsulated agent
- Site avoidance effect.
- Improved pharmacokinetic effects (reduced elimination, increased circulation life times).
- Flexibility to couple with site specific ligands to achieve active targeting.
- Liposome is used for drug delivery systems due to its unique structural properties.
- Liposome can carry both the hydrophobic and hydrophilic drug. Therefore, liposome as a drug carrier can indiscriminately deliver drugs through the cell membrane.
- Liposome herbal therapy acts as a carrier for small cytotoxic molecules and as vehicle for macromolecules as gene.
- Liposome formulation can produce sustained and controlled release of formulation and enhances the drug solubility

Ethosomes: Ethosomes are non-invasive delivery carriers that permit drugs to achieve the deep skin layers and/or the systemic circulation. These are soft, malleable vesicles tailored for enhanced delivery of active agents. They are composed mostly of phospholipids, (phosphatidylcholine, phosphatidylserine, phosphatitidic acid), high concentration of ethanol and water. The high concentration of ethanol makes the ethosomes. [26] Ethosomes are soft lipid vesicles of size range from tens of nanometres to microns, Hence, size of

ethosomal vesicles increases with decrease in concentration of ethanol [27, 28].

Advantage [29]

- Ethosomes are improved penetration of drug through skin for transdermal and dermal delivery
- Ethosomes are stage for the delivery of huge and diverse group of drugs (peptides, protein molecules).
- Ethosomes composition is safe and the components are approved
- The Ethosomal system is inactive, non-invasive and is available for immediate commercialization.

Transferosomes: The term transferosome was given in 1991 by GregorCevc. Transferosomes means carrying body and is derived from Latin word transfer means carry across and the Greek word soma means body[30].Transferosomes have been broadly used as carrier for the controlled and targeted delivery of proteins, peptides, hormones and several drugs [31,32]. The oral delivery of peptides such as insulin and interferon is not possible due to their instability and rapid degradation in the harsh environment of gastro intestinal tract. Biogenic molecules such as insulin, vaccines, which are degraded in the gastrointestinal tract, can be administered through transferosomes. It consists of both hydrophilic and hydrophobic properties [33].

Enzymosomes: The therapeutic proteins like enzymes can be delivered through several approaches such as using polymeric carriers; aqueous space of lipid and bilayered vesicles but their delivery by attachment on surface of liposomes has shown the prominent response for the development of antibodies at the target site [34]. Liposomal constructs engineered to provide a mini bioenvironmental in which enzymes are covalently immobilized or coupled to the surface of liposomes. Targeted delivery to tumor cell [35] Enzymes upon complex with lipids produce enzymosomes. Superoxide Dismutase (a therapeutic agent for oxidative stress related diseases like rheumatoid arthritis and ischaemia (reperfusion situations) loaded enzymosomes have been developed with long circulation time in the blood, in order to accumulate at inflamed target sites, even as maintaining enzymatic activity in its intact form [34].

Pharmacosomes: The limitations of transfersomes can be overcome by the "pharmacosomes" approach. The prodrug conjoins hydrophilic and lipophilic properties, and therefore acquire amphiphiliccharacters, and related to other vesicle forming components, was found to decrease interfacial tension, and at superior concentrations exhibits mesomorphicbehaviour [36]. Because the system is formed by linking a drug (pharmakon) to a carrier (soma), they are called pharmacosomes. Pharmacosomes bearing unique advantages over liposome and noisome vesicles have come up as potential alternative to conventional vesicles [37].

Advantage [38, 39]

- It is an effective tool to achieve required therapeutic goals such as drug targeting and controlled release.
- High and predetermined entrapment efficiency as drug and carrier form a stoichiometrically defined unit covalently linked together
- Volume of inclusion doesn't influence entrapment efficiency.

Emulsomes: Emulsomes is a lipid based drug delivery system, especially designed for parenteral delivery of drugs having poor aqueous solubility [40]. Nanosize Lipid particles (bio adhesives nanoemulsion) consisted of microscopic lipid assembly with a polar core in emulsomes[39]. The internal core is made up of fats and triglycerides, which are stabilize in form of o/w emulsion by addition of high concentration of lecithin. Emulsomes have the characteristics of both liposomes and emulsions. By asset of solidified or semi solidified interior oily core, it provides better opportunity to load lipophilic drugs in high concentration, simultaneously a controlled release can also be expected and these also have the ability to encapsulate water soluble medicaments in aqueous compartments of surrounding phospholipids layers. The solvent-free and surfactant-free emulsomes technologies have demonstrated high encapsulation capacity for water insoluble antifungal and anticancer drugs, showed enhanced drug delivery and improved preclinical efficacy for oral route [4]. This study focus on preparing macrophage (liver, spleen and bone marrow) targeted Emulsomes to reduce the adverse effects of conventional treatments [41].

Sphinosomes: Sphingosomes may be defined as "concentric, bilayered vesicle in which an aqueous volume is completely enclosed by a membranous lipid bilayer mostly composed of natural or synthetic sphingolipid [41]. Liposome stability problems are of course much more severe so it is very important task to improve the liposomal stability. Liposomal phospholipids can undergo chemical degradation such as oxidation and hydrolysis Hydrolysis of ester linkage will slow at pH value close to neutral. The hydrolysis may be avoided overall by use of lipid which contains ether

or amide linkage in its place of ester linkage phospholipids derivatives with the 2- ester linkage replaced by carbomoyloxy function **[**42]. Sphingosomes are administered in numerous ways these include parenteral route of administration such as intravenous, intramuscular, subcutaneous, and intra-arterial. Commonly it will be administered intravenous or different cases by inhalation [43]. In simple way we can state Sphingosomes is liposome which is composed of sphingolipid [44].

Advantage [42]

- It give the selective passive targeting to tumour tissue
- Increase efficiency and therapeutic index.
- Increase stability via encapsulation
- It diminishes in toxicity of the encapsulated agent.

Phytosomes: The term 'Phyto' means plant while 'Some' means cell-like. Phytosomes is vesicular drug delivery system in which phytoconstituents of herb extract enclose and bound by lipid (one phytoconstituents molecule linked with at least one phospholipid molecule) [45, 46]. Phytosomes is also called as Phytolipids delivery system which forms a bridge between the convectional delivery system and novel delivery system [46]. It is a recently introduced patented. Technology developed by Indena to incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes, which enhances their absorption and bioavailability[45,47]. The water soluble constituents (flavonoids and terpenoid) of plant extracts have the affinity to bind directly with phosphatidylcholine [48]. Phytosomes are advanced forms of herbal products that are better absorbed, utilized and as a result produce better results than conventional herbal extracts [49].

Niosomes: Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name niosomes. The niosomes are very small, and microscopic in size [50]. Niosomes or non-ionic surfactant vesicles are microscopic lamellar structure of size range 10- 1000nm consisting of spherical, uni or multilamellar and polyhedral vesicles in aqueous media. Their size lies in the nanometric scale [51]. They are vesicular systems similar to liposomes that can be used as carrier of amphiphilic and lipophilic drugs [52]. Niosomes have recently been shown to greatly increase transdermal drug delivery and also can be used in targeted drug delivery, and thus increased study in these structures can provide new methods for drug delivery [50].

Advantages of Niosomes

- Niosomes have capability biodegradable, biocompatible and non immunogenic to the body [53].
- Niosomes are used in the delivery of broad variety of drugs as it has capability to entrap hydrophilic, lipophilic as well as amphiphilic drugs [54, 55].
- Niosomes shows controlled and sustained release of drugs due to depot formation [55].
- Niosomes show a greater bioavailability than conventional dosage forms [56].
- Shape, size, composition, fluidity of niosomes drug can be controlled as and when required.
- Niosomes had been effectively used in targeting drugs to various organs [57].

Aquasomes: Aquasomes firstly developed by Kossovsky, are one of the most recently developed delivery system for bioactive molecules [58]. Three layered self-assembly compositions with ceramics carbon nanocrystalline particulate core coated with, glassy cellobiose specific targeting and molecular shielding [59]. The solid core provides the structural stability, while the carbohydrate coating protects against dehydration and stabilizes the biochemically active molecules. Aquasomes are spherical 60- 300 nm size particles called Âbodies of water their water like properties protects and conserve fragile biological molecules [60]. Aquasomes can be used as vaccines for delivery of viral antigen, for targeted intracellular gene therapy, for delivery of insulin and enzymes like DNAase and pigments/dyes [61].

Bilosomes: Bilosomes are the novel innovative drug delivery carriers consist of deoxycholic acid incorporated into the membrane of niosomes [62]. As conventional vesicles (liposomes and niosomes) can cause dissolution and undergo enzymatic degradation in gastro intestinal tract but incorporation of bile salts (commonly used penetration enhancers) in niosomal formulation could stabilize the membrane against the detrimental effects of bile acids in GI tract [5, 61]. These bile salt stabilized vesicles are known as bilosomes. These are highly biocompatible and have been found to improve the therapeutic efficacy of drugs due to their stability in gastro intestinal tract. Bilosomes have been found to increase the bioavailability of drugs as they can readily absorbed through small intestine to the portal circulation (hepatocirculation). Through this circulation they approach to liver and release the drug, so found to be an effective tool in drug targeting to liver [63].

USES OF VESICULAR DRUG DELIVERY SYSTEM IN LIVER DISEASES

Liver diseases: Liver play a vital role in regulation of physiological processes. It is involved in several very important functions such as metabolism, secretion and storage. Furthermore, detoxification of a variety of drugs and xenobiotics occur in liver. The bile secreted by the liver has, among other things, an important role in digestion. Liver diseases are among the mainly serious ailment [64,65]. They may be classified as acute or chronic hepatitis (inflammatory liver diseases) hepatosis (non-inflammatory diseases) and cirrhosis (degenerative disorder resulting in fibrosis of the liver). Liver diseases are chiefly caused by toxic chemicals (certain antibiotics, chemotherapeutics, peroxidised oil, aflatoxin, carbon-tetrachloride, chlorinated hydrocarbons, etc.), excess consumption of alcohol, infections and auto immune disorder. Mainly of the hepatotoxic chemicals damage liver cells mainly by inducing lipid peroxidation and other oxidative damage in liver. Enhanced lipid peroxidation produced during the liver microsomal metabolism of ethanol may result in hepatitis and cirrhosis **[**66].

Liver toxicity inducing agents

Carbon tetrachloride (CCl_4): Liver damage due to CCl_4 in rats was first reported in 1936 [67] and has been extensively and successfully used by many investigators [68, 69]. Carbon tetrachloride is metabolized by cytochrome P-450 in endoplasmic reticulum and mitochondria with the arrangement of CCl_3O a reactive oxidative free radical, which initiates lipid peroxidation [70, 71]. Administration of a single dose of CCl_4 to a rat produces, within 24 hrs, a centrilobular necrosis and fatty change. The poison reaches its maximum concentration in the liver within 3 hrs of administration. After that, the level falls and by 24 hrs there is no CCl_4 absent in the liver [72]. The growth of necrosis is associated with leakage of hepatic enzymes into serum. Dose of CCl_4 that induces hepatotoxicity ranges from 0.1 to 3 ml/kg administered intraperitoneally [73].

Thioacetamide: Thioacetamide interferes with the movement of RNA from the nucleus to cytoplasm which may cause membrane injury. A metabolite of thioacetamide (perhaps S-oxide) is responsible for hepatic injury. Thioacetamide reduce the number of viable hepatocytes as well as rate of oxygen consumption. It also decrease the volume of bile and its content i.e. bile salts, cholic acid and deoxycholic acid. Dose of thioacetamide is 100 mg/kg, subcutaneous [74].

Paracetamol: Paracetamol, is broadly used analgesic and antipyretic drug, produces acute liver damage in high doses. Paracetamol administration cause necrosis of the centrilobular hepatocytes characterized by nuclear pyknosis and eosinophilic cytoplasm followed by large excessive hepatic lesion. Covalent binding of Nacetyl-P-benzoquinoneimine, an oxidative product of paracetamol to sulphydryl groups of protein, result in lipid peroxidative degradation of glutathione level and thereby produce cell necrosis in the liver. Dose of Paracetamol is 1 gm/kg Post oral [75].

Uses of vesicular drug delivery system liver diseases

Reduction of drug side effect: Vesicular drug as a tool of targeting therapy in liver diseases is still in a stage of preclinical examination. Vesicular targeted therapy should theoretically recover treatment outcome as well as reduce adverse effects. With liposome- encapsulated phosphatidyldideoxycytidine (DOP-ddC) for treatment of hepatitis B virus, [76]. Marked adverse effects of anti-tumours agents, such as cisplantin, usually impede their applications in patients with malignancies. The toxicity of vesicular drug encapsulated cisplantin was significantly reduced, whereas its therapeutic effects were achieved in a recent study in rodents [77, 78**].** The immunosuppressive efficacy of the CsA-liposomes was improved with a higher survival rate of transplanted livers. Thus, the encapsulated agent had a longer circulating time, lower plasma concentration, and a similar or better therapeutic efficacy [77]. Therefore, vesicular drug encapsulation, which reduces toxicity of drugs by altering their pharmacokinetics and disposition, may be a potentially effective modality in clinical settings [79].

Study of Kupffer cell function: vesicular system are a helpful tool for the study of Kupffer cell function both in physiological and pathological situations due to the high rate of vesicular drug incorporation in these cells. Kupffer cell in vivo function can be evaluated by selectively targeting agents to the cells that will whichever improve or inhibit their activity [80, 81, 82]. Which are encapsulated in vesicular drug. Vesicular drug can be readily employed to decrease toxicity of therapeutic agents to other organs, while at the same time enhancing the drug concentration that is seen by the liver. Because Kupffer cells have newly been shown to play crucial roles in the pathophysiology of hepatic injury and fibro genesis, the tendency of vesicular drug to target this specific cell type becomes even more beneficial [79].

Reduction of hepatotoxins-induced liver damage: Reduce of hepatotoxins induced liver injury by vesicular drug targeted system. Lipid peroxidation is involved in liver injury induced by carbon tetrachloride (CCL_4,) and other chemicals. Intravenous injection of vitamin E containing-vesicular drug has been shown to be highly effective in the treatment of the damage, probably by means of the anti-oxidant effect of vitamin E [83]. Numerous drugs which display toxicity to the liver, such as acetaminophen, may elicit lipid peroxidation. Metabolism of ethanol may also evoke oxidant insult to the liver. Thus, Vesicular drug –targeting system anti-oxidant treatments, e.g., vitamin E and its analogues (trolox C, TGPS), or superoxide dismutase (SOD) [84], may benefit patients with drug-associated liver damage or alcoholic liver disease [79, 85].

Gene therapy: Cationic liposomes are convenient carriers for in vivo gene transfer and there is a list of hepatic diseases or disorders that might be appropriate for gene therapy via liposome targeting; the list includes viral hepatitis, metabolic disorders such as a,-antitrypsin (a,-AT) deficiency, and hepatic malignancies. Features of cat- ionic liposomes allow for a high entrapment rate of polynucleotide's and efficient transfer, which may improve the expression of transferred genes [76, 77, 86]. For example, a plasmid which contained human a,- AT gene sequences and was entrapped in small liposomes composed of EPC, brain phosphatidylserine and cholesterol, has been moved into mouse hepatocytes, and the expression of human a,-AT was identified in the liver of the transgenic mice [78].

CONCLUSION

This article outlines about Liposomes, Emulsomes, Enzymosomes, Ethosomes, Sphingosomes, Transferosomes, Pharmacosomes, Niosomes Bilosomes, and Aquasomes Vesicular systems. The vesicular delivery systemsgive many advantages such as increasing bioavailability, targeting and better stability in delivering drugs. Since, it has many advantages over the conventional medicine, vesicular mode of delivery can be used for efficient targeting of liver, liver regulation of physiological process. It is involved in several vital functions such as storage, secretion, metabolism and detoxification of a variety of drugs and xenobiotics. Liver diseases are mainly caused by either toxic chemicals (certain antibiotics, peroxides oil, aflatoxin, carbon tetrachloride chlorinated hydrocarbons etc), excess consumption of alcohol, infections or autoimmune disorder.

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