|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of vesicles** | **Model drug** | **Composition** | **Results** | **Reference** |
|  |  |  |  |  |
| **Liposomes** | Silybin (SLB) | HBVpreS/2-48myr (HBVP) conjugated to PEGylated liposomes (HBVP-Lip) | Through a receptor-mediated endocytosis gateway, a considerably more significant quantity of HBVP Lip was gobbled up by primary mouse hepatocytes. In vivo and in vitro, the system demonstrated a high level of specificity and efficacy in hepatic cell attacking. After intravenous injection of HBVP-Lip, interim safety studies indicated that neither acute immunotoxicity nor systemic toxicity was found. Altogether, the findings suggested that the HBVP-Lip might be a prospective ubiquitous and secure hepatotropic transporter for a wide range of compounds, opening up new possibilities for liver-specific delivery methods for bio-imaging agents, genes, and medications. | [88] |
| **Liposomes** | - | siRNAs/polyanion-containing hepatotropic lipoplexes modified with guanidinopropyl (GP) | The surface charge was found to be +65 mV, and a median diameter of 50–200 nm was discovered. Without showing any signs of toxicity, good suppression of viral replication indicators was detected. The system's effectiveness was greatly improved, whereas formulations containing chemically altered siRNAs became less immunostimulatory. HBVmRNA breakage happened in vivo at the anticipated target location, indicating that the process was RNAi-mediated. These findings suggested that the constructed system successfully silenced HBV replication in vivo and could treat HBV infection. | [89] |
| **Nanoparticles** | - | Plasmonic gold NPs (AuNPs)/ layered double hydroxide self-assemblies (LDHs) (AuNPs/LDHs) | Several AuNPs/LDHs evaluated decreased the number of subviral and viral particles generated by cured cells by up to 80% and were cytocompatible. The less cytotoxic plasmonic and antiviral features of the framework nanocomposites suggest that they have the capability to be tuned as new effective treatment options for hepatitis B. | [90] |
| **Nanoparticles** | - | Cationic poly (D,L-lactic-co-glycolic acid) PLGA/ IFN-α coated HBsAg | The results indicated that after 4 hours of administration, 75% of the radioactivity was retrieved in the liver, which was roughly 3-fold more than the ordinary PLGA nanoparticles. The bioavailability of IFN nanoparticles shows that they are resistant to RES and can propagate in the blood for a prolonged duration. The formulation's intravenous/subcutaneous delivery may enhance patient compliance by lowering dose frequency from traditional doses, resulting in healthier hepatitis B care. | [91] |
| **Micelles** | - | Stearic acid grafted chitosan oligosaccharide (CSSA)/ DrzBC (CSSA/DrzBC) | The system had a significantly reduced cytotoxicity and a better targeting capacity in subcellular organelles-cytoplasm. The system also exhibited a maximum IR of 82.51 ± 1.28% at 72 hours. Across every concentration, DrzBC carried by CSSA micelles had a larger IR of HBeAg expression over DrzBC supplied by LipofectamineTM2000, which could lead to the molecular target in the cytoplasm. Overall, the findings showed that the CSSA/DrzBC complicated nanoparticles could be helpful in anti-HBV gene therapy. | [92] |
| **Exosomes** | - | HBx/ mRNA/ protein incorporated into exosomes | The HBx-expressing cells secreted more exosomes, according to the nanoparticle tracking study, and confocal examinations verified that HBx with CD63 and CD9 were co-localized. The exosomal cargo produced by HBx-expressing cells had a significant impact on receiving hepatic cells, enabling the establishment of a favorable environment for cellular transition. Exosomal regulation by HBx may also be therapeutically relevant because the detection of viral elements in exosomes obtained from the patient's serum can be utilized to determine the phase and severity of the disease. | [93] |
| **Nanoparticles** | - | unmethylated cytosine-phosphate-guanosine oligodeoxynucleotides (CpG ODNs) from HBV genome (HBV-CpG)/ nanoparticles NP(HBV-CpG) | HBV-ODNs were able to suppress HBV CpG-induced IFN- α development. In mice inoculated with NP(HBV-CpG) and rHBsAg, the strategy boosted the immune response towards HBsAg and shifted it toward the Th1 axis. Furthermore, in HBV-bearing mice, the system-based treatment resulted in effective HBV clearance as well as an anti-HBsAg reaction. In conclusion, the system was a promising pharmacological tool for the management of CHB infection. | [94] |

**Supplementary Table I** Recent novel formulations including nano-drug delivery systems for the therapy of Hepatitis B [88-94].