Study Progress in the Application of Liposome as a Bone-Targeting Drug Carrier

Jian Wang¹, *, Yan Duan¹, Changpeng Xu², Li Gong³, Yu Zhang¹, Limin Cen¹, and Qiwen Sun¹

¹Inner Mongolia Autonomous Region People's Hospital Hohhot Inner Mongolia 010010
²Guangdong Second People's Hospital, Hohhot, Inner Mongolia 510050, China
³Southern Medical University Guangzhou Guangdong 510050

*Corresponding author: Inner Mongolia Autonomous Region People's Hospital 136399711@qq.com

Keywords: Bone-targeting drug; Liposome carrier; Application study

Abstract: As a carrier of bone-targeting drug, liposome has a wide prospect with advantages of increasing the drug effect and less toxic by-effect. After modified by various mechanisms, liposome can carry drugs by active targeting, passive targeting and dual targeting etc. methods and deposits in bones to allow the drug selectively acts on the bone tissue. Currently the active targeting liposome is the key point of clinical study, which means to chemically modify the liposome surface in chemical way, and increase the bone-affinity of liposome. This study basing on the statement above, summarized the application of different liposome carrier drugs, and make a prospect of liposome application.

The ideal targeting drug should have the requires of specific targeting less toxic by-effect, easy to degrade without accumulating, biochemical stability, non-immunogenicity, and can release the active ingredient of the drug at the expected rate. Liposomes belong to the new drug carrier, which originated from the experimental study of phospholipid suspension water [1], belonging to orientation arranged phospholipid bimolecular microspheres, similar to the structure of the biofilm, are artificially prepared encapsulated fat-soluble and water-soluble drug carriers. Liposomes have the advantages of changing the route of administration, prolonging the efficacy, promoting drug targeting of the reticuloendothelial system, reducing toxicity and tolerance etc., especially in recent years, as an effective carrier for bone-targeting drugs, which have the advantages that traditional drugs don't have, therefore it was widely concerned by pharmaceutical research. According to the difference of targeting mechanism, bone-targeted liposomes can be divided into active, passive and dual bone-targeting liposomes. The three liposomes will be discussed in detail below.

1. Preparation of Active Bone-Targeting and Drugs Application

As an encapsulated fat-soluble and water-soluble drug carrier, liposome itself does not have specific targeting. It is necessary to equip the homing device above the lipid bilayer to impart tissue specificity. The liposome surface is chemically modified with chemical methods to give it a bone-like property. From the perspective of structural analysis, the calcium in human bones is mainly distributed in the form of hydroxyapatite. The calcium content in the bone accounts for 99% of the total calcium content of the human body, and the other 1% is distributed in the extracellular fluid and other soft tissues of the human body. And is intrinsically different from the form of hydroxyapatite, so any molecule that specifically binds to hydroxyapatite can be used as a bone targeting inducer to allow chemically modified liposomes to carry, and plays a specific targeting role in bone tissue.

1.1 Preparing Methods.

The hydroxyapatite in the bone formation region shows a low crystalline form, while the bone resorption region shows a high crystalline form, the hydroxyapatite can bind to the repeated amino acid sequence in the oligopeptide, and the affinity of the different crystalline forms of the
hydroxyapatite shows the difference manifested by the amino acid sequence. For example, the oligopeptide and bone resorption region composed of 6 times repeated aspartic acid-serine-serine sequence have a strong affinity with the hydroxyapatite. The aspartic acid octapeptide has a strong affinity with the high crystalline form of hydroxyapatite. According to this feature, some oligopeptide-liposome \[2\] is prepared by freeze-drying method by scholars, which can specifically bind to low crystalline mineral salts in the bone formation area, thereby enabling targeting transmission of small nucleic acids to osteoblasts; vivo experiments have shown that oligopeptide-liposomes have specific targeting effects on bone formation regions \[3\]. Therefore, by utilizing the similarities and differences of the crystalline forms of hydroxyapatite, the specific targeting of bone resorption or bone formation regions can be controlled by the affinity of some molecules for different crystalline forms. Hongmei Zhang \[4\] et al. prepared a hydroxyapatite-coated liposome using a liposoluble drug such as indomethacin, which has a longer release time than a liposome without a coating and has a dual effect on bone targeting and sustained release.

Except the ideal specific binding target of hydroxyapatite, liposomes can also play an active targeting role in bone through other methods. For example, some anionic phospholipids contained in liposomes can be used as markers of apoptotic cells. It can bind to specific receptors of macrophages. According to this feature, the active targeting effect of modified liposomes on macrophages can be realized by the phagocytic mechanism of macrophages. The modified liposome is only phagocytosed by macrophages distributed to the bone marrow to avoid being ingested by hepatosplenic macrophages, so liposomes also have prospect applications as bone targeting conducting systems.

1.2 Application of Bisphosphonate Bone Resorption Inhibitor.

Bisphosphonates are typical bone resorption inhibitors and show strong affinity for hydroxyapatite. The modification of bisphosphonate molecules can increase the affinity of liposomes, such as Linlin Liu \[5\] et al. used a synthetic target consisting of a bisphosphonate and a new amphiphilic molecule recognizes and binds hydroxyapatite and prepares a target-modified liposome for bone targeting conduction. This study demonstrates that the modified bisphosphonate distributed on the surface of the liposome promotes the binding of hydroxyapatite and liposome. In addition, Xin Wang \[6\] et al. modified the liposome with a synthetic bis phosphoric acid derivative CHOL-TOE-BP (cholesterol-trioxyethylene-bis phosphoric acid), the cholesteryl of the derivant embedded the bilayer of liposome, the bis phosphoric as a target partially covers the lipid bilayer, and the molecular mechanism by using C2HCl3 to link the space can impart bone targeting property to the liposome, and after the drug is carried to the target tissue through the liposome, the drug can be fully extended, and the local drug concentration is increased, which is beneficial to reduce systemic by-effects.

The stannous methylene diphosphate has natural bone affinity property, and Xiaopeng Qu \[7\] et al. used this feature to cross-link it with doxorubicin liposome to prepare stannous methylene diphosphate-doxorubicin liposome, which can change the pharmacokinetic distribution feature of doxorubicin liposomes. Compared with conventional doxorubicin, cross-linked liposomes have a targeted inhibition mechanism for osteosarcoma, and the anti-tumor effect is significantly improved and adverse reactions is obvious reduced. Except the bisphosphonates, tetracyclines, small molecule heterocycles, and small peptide compounds can specifically bind to the hydroxyapatite, and thus all can be used for liposome cross-linking to prepare bone targeting drugs.

2. Passive Bone Targeting Liposome Preparation and Drug Application

Passive bone targeting liposome refers to a liposome that after taken up by the mononuclear macrophage system in vivo, the liposome is concentrated in the bone under normal physiological conditions. Due to the distribution of specific macrophages in the human bone marrow, small cells and special particles in the blood circulation can be adsorbed into the bone marrow by phagocytic mechanism, and the ability to utilize bone marrow macrophages allows liposomes to be specifically phagocytosed and aggregated in bone. In the bone aggregation, to achieve passive bone targeting
medication, the key point is the effect of strong phagocytic ability of macrophages on liposome production in hepatosplenic macrophages and bone marrow-blood circulation barrier, but the microparticles whose size <100nm can pass through the bone marrow-blood circulation barrier. The microparticle system of 0.1~0.2 μm particle size will be quickly cleared by the macrophages of the reticuloendothelial system and eventually enter the lysosome of the liver Kupffer cell, while the microparticle whose size<50nm can penetrate the liver endothelial cells, or reach the spleen and bone marrow through lymphatic transmission. Therefore, reducing the particle size is the key to inhibit the uptake of liposomes by the liver and spleen and increase the amount of aggregation in the liposome bone.

The blank liposome prepared by freeze-drying method can be combined with the meglumine stibiate solution to obtain small-sized meglumine stibiate liposome, and Schettini D A [8] et al. conducted experiments in vivo to investigate the effects of pharmacokinetics and liposome particle size on bone targeting. The results showed that the small particle size and high encapsulation ratio of meglumine stibiate liposome could maintain high concentration of expectorant in bone tissue compared with the large particle size liposome and free drug, and the bone targeting property is improved. For the liposome having the same composition, the smaller the particle size is, the higher the bone targeting property is in the range of 300 to 2000 nm. However, particle size is not the only factor determining the distribution of liposomes in vivo. The surface hydrophobicity, electric charge and liposome composition of liposomes affect the distribution of liposomes in vivo as well. How to control the effects of these factors to change the liposome distribution in vivo and improve bone targeting still needs further research.

3. Dual Bone Targeting Liposome Preparation and Drug Application

Liposomes prepared by both active and passive bone targeting mechanisms at the same time are called dual bone targeting liposomes, and dual bone targeting liposomes have higher bone targeting property than liposomes prepared using single mechanism. Qun Su [9] found that flexible liposomes have unique deformation feature, which can pass through the pore size smaller than the flexible liposome without rupture, thus promoting more particles through the bone marrow - blood circulation barrier to have bone targeting effect, while using hydroxyapatite as a target, flexible nanoliposomes prepared according to the above mechanism have active and passive dual bone targeting property. Jia Guo [10] et al. prepared EDTMP, 12-EDTMP, poloxamer 407 modified flexible nanoliposomes, comparing with the unmodified ordinary flexible nanoliposomes, and the modified 3-bone nanoliposomes had a total bone targeting efficiency increase of more than 500%. Sou K [11] et al. prepared liposomes modified with 5-hexadecyl ester, L-glutamic acid and N-[3-carboxy-1- propylene oxide]-1, that is, SA-Ve, and conducted rabbit animal experiments, the results showed that the preparing objects all had bone targeting property. After 24 hours of intravenous injection, the prepared liposomes were mainly distributed in the liver and bone marrow, while the common liposomes were distributed in the liver and spleen, after further modification with polyethyleneglycol, the liver intake of 5-hexadecyl ester and ordinary liposome was significantly reduced, and when the incorporated polyethyleneglycol reached 0.6%, the distribution amount of SA-Ve in the bone marrow peaked, indicating that SA-Ve has bone targeting property. However, the above test also shows that the liver has an inter-competing mechanism for the intake ability of bone marrow liposomes, and an appropriate amount of polyethyleneglycol indicates that the modification can inhibit this mechanism, and directing SA-Ve to distribute in the bone marrow. This process can be viewed as an active binding dual-passive dual targeting. Based on the above studies, Kawaguchi AT [12] et al. discussed the bone targeting feasibility of SA-Ve in an animal experiment on macaques. The results showed that bone marrow macrophages can take up 70% of SA-Ve after intravenous administration. This study further increases the feasibility of this type of liposome as a clinically specific bone targeting drug carrier.
4. Conclusion

From what had been mentioned above, liposome study as a bone targeting drug carrier provides a good platform for clinical treatment of bone tumors, osteoporosis and other diseases, but in addition to bone targeting, liposome stability and drugs sustained release property will affect the liposome drug delivery targeting mechanism. Therefore, in order to develop an ideal bone targeting liposome drug, it is still necessary to explore the influencing factors of liposome distribution in vivo, and further study is needed.

Acknowledgement

Project Source: National Natural Science Foundation of China Project No. 81560368

References


