CLAIMS

1. An actively encapsulating liposome nanocarrier delivery system, wherein the liposome nanocarrier delivery system comprises a liposome carrier and a substance used for preventing and/or treating atherosclerosis or an atherosclerosis-related disease actively encapsulated by the liposome carrier, wherein the materials of the liposome carrier comprise phospholipid and cholesterol; the liposome nanocarrier delivery system is modified with a targeting ligand which is hyaluronic acid and DSPE-PEG2000-NH_2 coupled through an amide bond; and in the liposome nanocarrier delivery system, the final concentration of the targeting ligand is 10-100μg/mL.

2. The liposome nanocarrier delivery system according to claim 1, wherein the phospholipid is one or more selected from the following: hydrogenated soybean phosphatidylcholine, distearoylphosphatidylcholine, distearoylphosphatidylethanolamine, polyethylene glycol-distearoylphosphatidylethanolamine, distearoylphosphatidylglycerol, distearoylphosphatidylserine, dioleoylphosphatidylcholine, dioleoylphosphatidylethanolamine, dioleoylphosphatidylserine, dioleoylphosphatidylethanolamine-polyethylene glycol, dicinnamoylphosphatidylcholine, dicinnamoylphosphatidylethanolamine, dicinnamoylphosphatidylserine, dicinnamoylphosphatidylethanolamine-polyethylene glycol, dipalmitoylphosphatidylcholine, dipalmitoylphosphatidylethanolamine, dipalmitoylphosphatidylserine, dipalmitoylphosphatidylethanolamine-polyethylene glycol, dierucoylphosphatidylcholine, dierucoylphosphatidylethanolamine, dierucylphosphatidylserine, dierucylphosphatidylethanolamine-polyethylene glycol, sphingomyelin, egg phosphatidylcholine, egg phosphatidylethanolamine, and egg phosphatidylglycerol.

3. The liposome nanocarrier delivery system according to claim 1 or 2, wherein the mass ratio of the substance used for preventing and/or treating atherosclerosis or an atherosclerosis-related disease to the liposome carrier is 1:0.1 to 50, 1:0.2 to 30, or 1:0.5 to 20.

4. The liposome nanocarrier delivery system according to any one of claims 1-3, wherein the substance used for preventing and/or treating atherosclerosis or an atherosclerosis-related disease is a weakly acidic substance; or

wherein the substance used for preventing and/or treating atherosclerosis or an atherosclerosis-related disease is one or more selected from the following: statins, fibrates, antiplatelet drugs, PCSK9 inhibitors, anticoagulant drugs, angiotensin converting enzyme inhibitors, calcium ion antagonists, MMPs inhibitors, β-receptor blockers, glucocorticoid, and pharmaceutically acceptable salts thereof; or

wherein the substance used for preventing and/or treating atherosclerosis or an atherosclerosis-related disease is one or more selected from the following: lovastatin, atorvastatin, rosuvastatin, simvastatin, fluvastatin, pitavastatin, pravastatin, bezafibrate, ciprofibrate, gemfibrozil, aspirin, acemetacin, sodium ozagrel, beraprost sodium, tirofiban, or pharmaceutically acceptable salts thereof; or

wherein the substance used for preventing and/or treating atherosclerosis or an atherosclerosis-related disease is water-soluble statins, alternatively rosuvastatin, pravastatin or atorvastatin.

5. The liposome nanocarrier delivery system according to any one of claims 1-4, wherein the average molecular weight of hyaluronic acid is 12,000 to 16,000.

6. The liposome nanocarrier delivery system according to any one of claims 1-5, wherein in the liposome nanocarrier delivery system, the final concentration of the targeting ligand is 100±24μg/mL.

7. The liposome nanocarrier delivery system according to any one of claims 1-6, wherein the liposome carrier is selected from small unilamellar liposomes, large unilamellar liposomes or multilamellar liposomes.

8. The liposome nanocarrier delivery system according to claim 1, wherein the atherosclerosis-related disease is one or more selected from the following: coronary atherosclerotic heart disease, cerebral atherosclerosis and peripheral vascular atherosclerosis.

9. The liposome nanocarrier delivery system according to claim 1, wherein the materials of the liposome carrier comprise phospholipid, cholesterol and DSPE-PEG2000.

10. A method of preparing the liposome nanocarrier delivery system according to any one of claims 1-9, comprising a step of hydrating the liposome carrier by adding a salt solution and performing separation to form a solution acidity gradient between inside and outside of the liposomes.

11. The method for preparing the liposome nanocarrier delivery system according to claim 10, wherein the salt is a salt of a weak acid and a strong alkali; and/or

wherein the anionic portion of the salt is one or more selected from the following:

acetate, edetate, bicarbonate, hypochlorite, citrate, benzoate and gluconate; and/or

wherein the cationic portion of the salt is one or more selected from the following: calcium ions, copper ions, nickel ions, barium ions, magnesium ions and zinc ions; and/or

wherein the salt is one or more selected from the following: calcium acetate, calcium bicarbonate, magnesium citrate and copper gluconate.

12. The method of preparing the liposome nanocarrier delivery system according to claim 10 or 11, wherein the method comprises the following steps:

(1) dissolving the liposome carrier material in a solvent;

(2) adding a salt solution that forms a solution acidity gradient between inside and outside of the liposomes to the product obtained in step (1) to hydrate and disperse it into a crude lipid solution;

(3) reducing the particle size of the crude lipid solution obtained in step (2) to obtain refined liposomes;

(4) purifying the refined liposome solution obtained in step (3) to remove external ions, and forming an acidity gradient between inside and outside of the liposomes; and

(5) adding a solution of the substance to be encapsulated to the liposome solution obtained in step (4), and performing incubation to allow the drug to enter the interior of the liposomes to obtain the liposome nanocarrier delivery system.

13. The method according to claim 10, wherein

i) the step (1) further comprises a step of removing the solvent by evaporation to make the liposomes form a lipid membrane;

optionally wherein the evaporation temperature is 40-80°C, preferably 50-70°C, or 50-60°C;

optionally wherein the evaporation method is rotary evaporation; and

optionally wherein the rotary evaporation is performed at a speed of 50-200 r/min, alternatively 70-120 r/min, yet alternatively 80-100 r/min; and/or

ii) in step (1), the solvent is one or more selected from the following: chloroform, ethanol, methanol, methylene chloride, acetone, toluene, diethyl ether, ethyl acetate, methyl acetate, acetonitrile, and dichloroethane.

14. The method according to any one of claims 12-13, wherein in step (1), the phospholipid is at a concentration of 0.1-500 mg/mL, preferably 0.1-200 mg/mL, or 0.2-100 mg/mL; and/or

the cholesterol is at a concentration of 0.05-200 mg/mL, preferably 0.1-100 mg/mL, or 0.1-50 mg/mL.

15. The method according to any one of claims 12-14, wherein in step (2), the salt solution has a concentration of 100-500 mM, preferably 200-300 mM, or 200-250 mM; and/or

the hydration temperature is 30-90°C, preferably 40-80°C, or 45-65°C.

16. The method according to any one of claims 12-15, wherein in step (3), the method of reducing the particle size is extruding the crude lipid solution through a filter membrane;

optionally, wherein the filter membrane is a polycarbonate membrane; and/or

wherein the filter membrane has a pore size of 30-800 nm, 50-400 nm, 100-200 nm, 30 nm, 50 nm, 100 nm, 200 nm, 400 nm, 600 nm or 800 nm, or 100-150 nm.

17. The method according to any one of claims 12-16, wherein in step (4), the method of removing external ions is one or more selected from the following: separation through an ultrafiltration membrane pack, dialysis separation and ion exchange.

18. The method according to any one of claims 12-17, wherein in step (5), the solution of the substance to be encapsulated is at a concentration of 0.01-100 mg/mL, 0.05-50 mg/mL, 0.1-20 mg/mL, or 0.1-10 mg/mL.

19. The method according to any one of claims 12-18, wherein in step (5), the incubation temperature is 20-80°C, 40-70°C, or 55-65°C.

20. The method according to any one of claims 12-19, wherein when the liposome nanocarrier delivery system is modified with a targeting ligand, the method further comprises the following step:

(6) co-incubating the targeting ligand with the liposome nanocarrier delivery system obtained in step (5) to obtain a modified liposome nanocarrier delivery system.

21. A medicine, wherein the medicine comprises the nanocarrier delivery system according to any one of claims 1-9 or the nanocarrier delivery system prepared by the method according to any one of claims 10-20, and a pharmaceutically acceptable carrier.

22. Use of the nanocarrier delivery system according to any one of claims 1-9, the nanocarrier delivery system prepared by the method according to any one of claims 10-20, or the medicine according to claim 21 in the manufacture of a medicament for preventing and/or treating atherosclerosis or an atherosclerosis-related disease;

optionally wherein, the atherosclerosis-related disease is one or more selected from the following: atherosclerosis, coronary atherosclerotic heart disease (including acute coronary syndrome, asymptomatic myocardial ischemia—latent coronary heart disease, angina pectoris, myocardial infarction, ischemic heart disease, sudden death, and in-stent restenosis), cerebral atherosclerosis (including cerebral ischemic stroke and hemorrhagic apoplexy), peripheral vascular atherosclerosis (including carotid atherosclerosis, vertebral atherosclerosis, subclavian atherosclerosis, occlusive peripheral atherosclerosis, retinal atherosclerosis, renal atherosclerosis, lower extremity atherosclerosis, upper extremity atherosclerosis, mesenteric atherosclerosis and atherosclerotic impotence), aortic dissection, hemangioma, thromboembolism, heart failure, and cardiogenic shock.

23. Use of the nanocarrier delivery system according to any one of claims 1-9, the nanocarrier delivery system prepared by the method according to any one of claims 10-20, or the medicine according to claim 21 in the manufacture of a medicament for treating vascular plaques;

optionally wherein the vascular plaques are arterial plaques;

optionally wherein the medicament is used to curb the progression of arterial plaques, reverse arterial plaques and/or reduce the volume of arterial plaques.