siRNA as a therapeutic agent, it is required to develop a delivery system that may stabilize siRNA in blood, efficiently deliver it into target cells or tissues, and yet not show toxicity.

【CONTENTS OF THE INVENTION】

【PROBLEMS TO BE SOLVED】

To resolve the problems described above, one object of the present invention is to provide a composition for delivering an anionic drug, comprising a micelle structure containing a salt of polylactic acid so as to effectively deliver anionic drugs into the body.

Another object of the present invention is to provide the use of the composition for delivering anionic drugs.

A further object of the present invention is to provide a method for delivering anionic drugs comprising administering the composition.

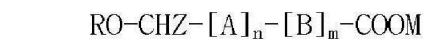
A still further object of the present invention is to provide a method for preparing a pharmaceutical composition capable of effectively delivering anionic drugs into the body.

【SUMMARY】

In one aspect, there is provided a composition for delivering an anionic drug, comprising: the anionic drug as an active ingredient; a cationic compound; an amphiphilic block copolymer; and at least one salt of polymer selected from the group consisting of the compounds of Formulae 1 to 6 as below;

wherein the anionic drug forms a complex with the cationic compound by electrostatic interaction; the complex is entrapped in the micelle structure of the amphiphilic block copolymer and the salt of polymer; and the surface charge of the micelle is from -20 to 20 mV

[Formula 1]

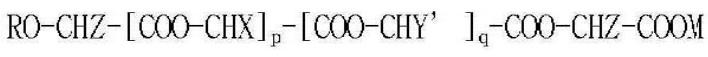


$RO-CHZ-[A]_n-[B]_m-COOM$

wherein A is -COO-CHZ-; B is -COO-CHY-, -COO-$CH_2CH_2CH_2CH_2CH_2$- or -COO-

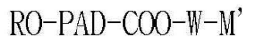
$CH_2CH_2OCH_2$; R is a hydrogen atom, or acetyl, benzoyl, decanoyl, palmitoyl, methyl or ethyl; Z and Y each are a hydrogen atom, or methyl or phenyl; M is Na, K or Li; n is an integer from 1 to 30; and m is an integer from 0 to 20;

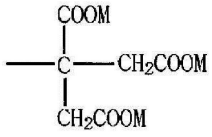
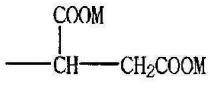
[Formula 2]



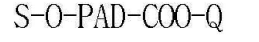
wherein X is methyl; Y' is a hydrogen atom or phenyl; p is an integer from 0 to 25, q is an integer from 0 to 25, with the proviso that p + q is an integer from 5 to 25; R is a hydrogen atom, or acetyl, benzoyl, decanoyl, palmitoyl, methyl or ethyl; M is Na, K or Li; and Z is a hydrogen atom, methyl or phenyl;

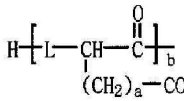
[Formula 3]



wherein W-M' is  or ; PAD is selected from the group consisting of D,L-polylactide, D-polylactide, polymandelic acid, copolymer of D,L-lactide and glycolic acid, copolymer of D,L-lactide and mandelic acid, copolymer of D,L-lactide and caprolactone, and copolymer of D,L-lactide and 1,4-dioxane-2-one; R is a hydrogen atom, or acetyl, benzoyl, decanoyl, palmitoyl, methyl or ethyl; and M is independently Na, K or Li;

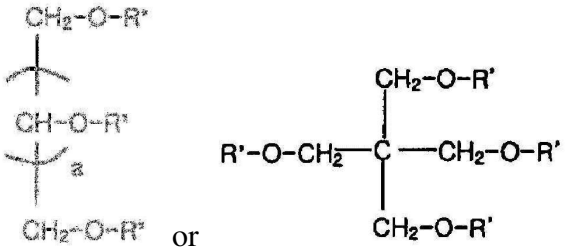
[Formula 4]



wherein S is ; L is $-NR_1-$ or -O-, wherein R_1 is a hydrogen atom or C_{1-10} alkyl; Q is CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, or $CH_2C_6H_5$; a is an integer from 0 to 4; b is an integer from 1 to 10; M is Na, K or Li; and PAD is at least one selected from the group consisting of D,L-polylactide, D-polylactide, polymandelic acid, copolymer of D,L-lactide and

glycolic acid, copolymer of D,L-lactide and mandelic acid, copolymer of D,L-lactide and caprolactone, and copolymer of D,L-lactide and 1,4-dioxane-2-one;

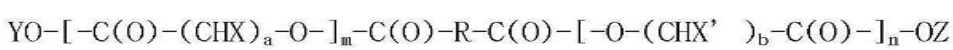
[Formula 5]



or

wherein R' is -PAD-O-C(O)-CH_2CH_2-C(O)-OM, wherein PAD is selected from the group consisting of D,L-polylactide, D-polylactide, polymandelic acid, copolymer of D,L-lactide and glycolic acid, copolymer of D,L-lactide and mandelic acid, copolymer of D,L-lactide and caprolactone, and copolymer of D,L-lactide and 1,4-dioxane-2-one, M is Na, K or Li; and a is an integer from 1 to 4; and

[Formula 6]



wherein X and X' are independently hydrogen, C_{1-10} alkyl or C_{6-20} aryl; Y and Z are independently Na, K or Li; m and n are independently an integer from 0 to 95, with the proviso that $5 < m + n < 100$; a and b are independently an integer from 1 to 6; and R is -$(CH_2)_k$-, C_{2-10} divalent alkenyl, C_{6-20} divalent aryl or a combination thereof, wherein k is an integer from 0 to 10.

In yet another aspect, there is provided a method for preparing the composition as described herein, comprising:

(a) dissolving an anionic drug, a cationic compound, an amphiphilic block copolymer and a salt of polymer in a water-miscible organic solvent or a mixed solvent of an aqueous solution and an organic solvent;

(b) removing a layer of organic solvent from step (a); and,

(c) adding an aqueous solution to the mixture from step (b) in which the organic solvent is removed, to form micelles

【TECHNICAL MEANS TO SOLVE THE PROBLEMS】

One embodiment of the present invention relates to a composition for delivering an anionic drug comprising a micelle structure containing a salt of polylactic acid so as to effectively deliver anionic drugs into the body, a use of the composition for delivering anionic drugs, and a method for delivering anionic drugs comprising administering the composition.

The composition for delivering an anionic drug containing the micelle structure according to an embodiment of the present invention comprises a micelle structure of an amphiphilic block copolymer and a salt of polylactic acid, which includes a complex of a drug

【CLAIMS】

【CLAIM 1】

A composition for delivering an anionic drug, comprising:

the anionic drug as an active ingredient;

a cationic compound;

an amphiphilic block copolymer; and

at least one salt of polymer selected from the group consisting of the compounds of Formulae 1 to 6 as below;

wherein the anionic drug forms a complex with the cationic compound by electrostatic interaction;

the complex is entrapped in the micelle structure of the amphiphilic block copolymer and the salt of polymer; and

the surface charge of the micelle is from -20 to 20 mV

[Formula 1]

$RO-CHZ-[A]_n-[B]_m-COOM$

wherein A is -COO-CHZ-; B is -COO-CHY-, $-COO-CH_2CH_2CH_2CH_2CH_2-$ or $-COO-CH_2CH_2OCH_2$; R is a hydrogen atom, or acetyl, benzoyl, decanoyl, palmitoyl, methyl or ethyl; Z and Y each are a hydrogen atom, or methyl or phenyl; M is Na, K or Li; n is an integer from 1 to 30; and m is an integer from 0 to 20;

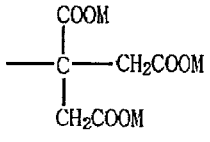
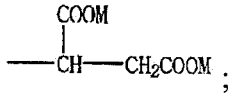
[Formula 2]

$RO-CHZ-[COO-CHX]_p-[COO-CHY']_q-COO-CHZ-COOM$

wherein X is methyl; Y' is a hydrogen atom or phenyl; p is an integer from 0 to 25, q is an integer from 0 to 25, with the proviso that p + q is an integer from 5 to 25; R is a hydrogen atom, or acetyl, benzoyl, decanoyl, palmitoyl, methyl or ethyl; M is Na, K or Li; and Z is a hydrogen atom, methyl or phenyl;

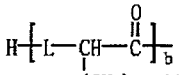
[Formula 3]

RO-PAD-COO-W-M'

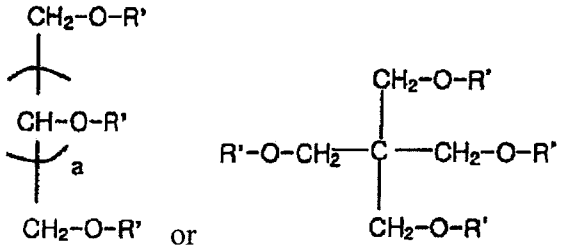
wherein W-M' is  or ; PAD is selected from the group consisting of D,L-polylactide, D-polylactide, polymandelic acid, copolymer of D,L-lactide and glycolic acid, copolymer of D,L-lactide and mandelic acid, copolymer of D,L-lactide and caprolactone, and copolymer of D,L-lactide and 1,4-dioxane-2-one; R is a hydrogen atom, or acetyl, benzoyl, decanoyl, palmitoyl, methyl or ethyl; and M is independently Na, K or Li;

[Formula 4]

S-O-PAD-COO-Q

wherein S is ; L is $-NR_1-$ or -O-, wherein R_1 is a hydrogen atom or C_{1-10} alkyl; Q is CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, or $CH_2C_6H_5$; a is an integer from 0 to 4; b is an integer from 1 to 10; M is Na, K or Li; and PAD is at least one selected from the group consisting of D,L-polylactide, D-polylactide, polymandelic acid, copolymer of D,L-lactide and glycolic acid, copolymer of D,L-lactide and mandelic acid, copolymer of D,L-lactide and caprolactone, and copolymer of D,L-lactide and 1,4-dioxane-2-one;

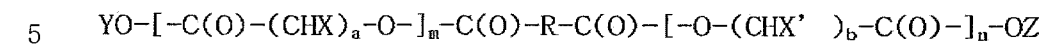
[Formula 5]



wherein R' is -PAD-O-C(O)-CH_2CH_2-C(O)-OM, wherein PAD is selected from the group consisting of D,L-polylactide, D-polylactide, polymandelic acid, copolymer of D,L-lactide and

glycolic acid, copolymer of D,L-lactide and mandelic acid, copolymer of D,L-lactide and caprolactone, and copolymer of D,L-lactide and 1,4-dioxane-2-one, M is Na, K or Li; and a is an integer from 1 to 4; and

[Formula 6]



$$YO-[-C(O)-(CHX)_a-O-]_m-C(O)-R-C(O)-[-O-(CHX')_b-C(O)-]_n-OZ$$

wherein X and X' are independently hydrogen, C_{1-10} alkyl or C_{6-20} aryl; Y and Z are independently Na, K or Li; m and n are independently an integer from 0 to 95, with the proviso that $5 < m + n < 100$; a and b are independently an integer from 1 to 6; and R is $-(CH_2)_k-$, C_{2-10} divalent alkenyl, C_{6-20} divalent aryl or a combination thereof, wherein k is an integer from 0 to 10.

【CLAIM 2】

The composition of Claim 1, wherein the anionic drug is a nucleic acid.

【CLAIM 3】

The composition of Claim 2, wherein the nucleic acid is at least one selected from the group consisting of RNA, DNA, siRNA (short interfering RNA), aptamer, antisense ODN (antisense oligodeoxynucleotide), antisense RNA, ribozyme and DNAzyme.

【CLAIM 4】

The composition of Claim 2 or 3, wherein the nucleic acid has at least one end modified with one or more selected from the group consisting of cholesterol, tocopherol and C_{10-24} fatty acid.

【CLAIM 5】

The composition of any one of Claims 1-4, wherein the cationic compound is at least one selected from the group consisting of a cationic lipid and a cationic polymer.

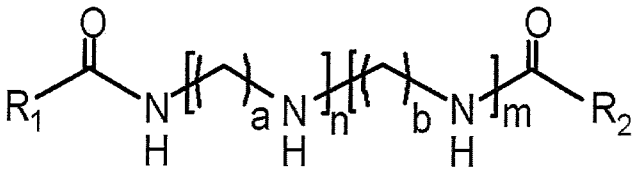
【CLAIM 6】

The composition of Claim 5, wherein the cationic lipid is at least one selected from the group consisting of N,N-dioleyl-N,N-dimethylammoniumchloride (DODAC), N,N-distearyl-N,N-dimethylammoniumbromide (DDAB), N-(1-(2,3-dioleoyloxy)propyl-N,N,N-trimethylammoniumchloride (DOTAP), N,N-dimethyl-(2,3-dioleoyloxy)propylamine (DODMA), 1,2-diacyl-3-trimethylammonium-propane (TAP), 1,2-diacyl-3-dimethylammonium-propane (DAP), 3β-[N-(N',N',N'-trimethylaminoethane)carbamoyl]cholesterol (TC-cholesterol), 3 β[N-(N',N'-dimethylaminoethane)carbamoyl]cholesterol (DC-cholesterol), 3β-[N-(N'-monomethylaminoethane)carbamoyl]cholesterol (MC-cholesterol), 3β-[N-(aminoethane)carbamoyl]cholesterol (AC-cholesterol), cholesteryloxypropane-1-amine (COPA), N-(N'-aminoethane)carbamoylpropanoic tocopherol (AC-tocopherol) and N-(N'-methylaminoethane)carbamoylpropanoic tocopherol (MC-tocopherol).

【CLAIM 7】

The composition of Claim 5, wherein the cationic lipid is represented by the following Formula 7:

[Formula 7]



wherein n and m each are 0 to 12 with the proviso that $2 \leq n + m \leq 12$, a and b each are 1 to 6, R_1

and R_2 each are independently selected from the group consisting of saturated and unsaturated C_{11-25} hydrocarbons.

【CLAIM 8】

The composition of Claim 7, wherein in the cationic lipid represented by Formula 7, n and m are independently 1 to 9, with the proviso that $2 \leq n + m \leq 10$.

【CLAIM 9】

The composition of Claim 7 or 8, wherein in the cationic lipid represented by Formula 7, a and b are 2 to 4.

【CLAIM 10】

The composition of any one of Claims 7-9, wherein in the cationic lipid represented by Formula 7 R_1 and R_2 each are independently selected from the group consisting of lauryl, myristyl, palmityl, stearyl, arachidyl, behenyl, lignoceryl, cerotyl, myristoleyl, palmitoleyl, sapienyl, oleyl, linoleyl, arachidonyl, eicosapentaenyl, erucyl, docosahexaenyl and cerotyl.

【CLAIM 11】

The composition of any one of Claims 5-10, wherein the cationic polymer is selected from the group consisting of chitosan, glycol chitosan, protamine, polylysine, polyarginine, polyamidoamine (PAMAM), polyethylenimine, dextran, hyaluronic acid, albumin, polymer polyethylenimine (PEI), polyamine and polyvinylamine.

【CLAIM 12】

The composition of any one of Claims 5-11, wherein the ratio of quantities of electric charges of the cationic lipid (N) and the anionic drug (P) (N/P) is 0.1 to 128.

【CLAIM 13】

The composition of any one of Claims 1-12, wherein the amphiphilic block copolymer is an A-B type di-block copolymer composed of a hydrophilic A block and a hydrophobic B block, wherein the hydrophilic A block is at least one selected from the group consisting of polyalkyleneglycol, polyvinyl alcohol, polyvinyl pyrrolidone, polyacrylamide and derivatives thereof, and the hydrophobic B block is at least one selected from the group consisting of polyester, polyanhydride, polyamino acid, polyorthoester and polyphosphazine.

【CLAIM 14】

The composition of Claim 13, wherein a hydroxyl group at the end of the hydrophobic B block is modified by at least one selected from the group consisting of cholesterol, tocopherol and C_{10-24} fatty acid.

【CLAIM 15】

The composition of Claim 13 or 14, wherein the hydrophilic A block has a number average molecular weight of 200 to 50,000 Dalton, and the hydrophobic B block has a number average molecular weight of 50 to 50,000 Dalton.

【CLAIM 16】

The composition of any one of Claims 5-15, wherein the ratio of the weight of the complex of the anionic drug and the cationic lipid (a) to the weight of the amphiphilic block copolymer (b) [a/b × 100] is 0.001 to 100 wt%.

【CLAIM 17】

The composition of any one of Claims 1-16, wherein the salt of polymer is represented by Formula 1 or Formula 2.

【CLAIM 18】

The composition of any one of Claims 1-17, wherein the salt of polymer has a number average molecular weight of 500 to 50,000 Dalton.

【CLAIM 19】

The composition of any one of Claims 1-18, comprising 10 to 1,000 parts by weight of the amphiphilic block copolymer and 5 to 500 parts by weight of the salt of polymer per 1 part by weight of the anionic drug.

【CLAIM 20】

The composition of any one of Claims 1-19 having the particle size of from 10 to 200 nm.

【CLAIM 21】

The composition of any one of Claims 1-20, further comprising a lyophilization aid.

【CLAIM 22】

The composition of any one of Claims 1-21, further comprising a fusogenic lipid.

【CLAIM 23】

The composition of Claim 22, wherein the fusogenic lipid is at least one selected from the group consisting of dilauroyl phosphatidylethanolamine, dimyristoyl phosphatidylethanolamine, dipalmitoyl phosphatidylethanolamine, distearoyl

phosphatidylethanolamine, dioleoyl phosphatidylethanolamine, dilinoleoyl phosphatidylethanolamine, 1-palmitoyl-2-oleoyl phosphatidylethanolamine, 1,2-diphytanoyl-3-sn-phosphatidylethanolamine, dilauroyl phosphatidylcholine, dimyristoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, distearoyl phosphatidylcholine, dioleoyl phosphatidylcholine, dilinoleoyl phosphatidylcholine, 1-palmitoyl-2-oleoyl phosphatidylcholine, 1,2-diphytanoyl-3-sn-phosphatidylcholine, dilauroyl phosphatidic acid, dimyristoyl phosphatidic acid, dipalmitoyl phosphatidic acid, distearoyl phosphatidic acid, dioleoyl phosphatidic acid, dilinoleoyl phosphatidic acid, 1-palmitoyl-2-oleoyl phosphatidic acid, 1,2-diphytanoyl-3-sn-phosphatidic acid, cholesterol and tocopherol.

【CLAIM 24】

A method for preparing the composition according to any one of Claims 1 to 23, comprising:

(a) dissolving an anionic drug, a cationic compound, an amphiphilic block copolymer and a salt of polymer in a water-miscible organic solvent or a mixed solvent of an aqueous solution and an organic solvent;

(b) removing a layer of organic solvent from step (a); and,

(c) adding an aqueous solution to the mixture from step (b) in which the organic solvent is removed, to form micelles.