Claims

1. A polyoxazoline (POZ) conjugate comprising a water-soluble POZ polymer and an agent linked to the water-soluble POZ polymer by a physiologically degradable linkage, or a pharmaceutically acceptable form thereof, wherein a release rate of the agent from the POZ conjugate is controlled by selecting a POZ polymer characteristic, an agent characteristic, a loading characteristic, or a combination of the foregoing.

2. The POZ conjugate of claim 1, wherein the agent is a phytocannabinoid, a dopamine agonist, an anticholinergic, a monamine oxidase-B inhibitor, a catechol-O-methyl transferase (COMT) inhibitor or an adenosine A_{2A} receptor antagonist, or a GABA-uptake inhibitor.

3. The POZ conjugate of claim 2, wherein the phytocannabinoid is selected from the group consisting of: cannabidiol, cannabigerol, cannabigerolic acid, cannabidiolic acid, cannabidiolmonomethylether, cannabidiol-C4, cannabidarinic acid, cannabidivarin, cannabidiol or cannabigerol propyl variant, cannabichromene, cannabichromenic acid, cannabichromevarinic acid, cannabichromevarin, cannabinol, cannabicyclol, tetrahydrocannabivarin, Δ^9-THC, ajulemic acid, and dexanabinol.

4. The POZ conjugate of claim 2, wherein the dopamine agonist is selected from the group consisting of: apomorphine, arbutamine, carbidopa, dobutamine, dopamine, entacapone, epinephrine, fenoldopam, isoetharine, isoproterenol, levopoda, levonordefrin, masaprocol, methyldopa, methyldopate, norepinephrine, protokylol, tolcapone, or (r)-(+)-fenoldopam, rotigotine, pramipexole, quinagolide, 5-OH-DPAT, ropinirole, pergolide, cabergoline, and bromocriptine.

~~5. The POZ conjugate of claim 2, wherein the anticholinergic is selected from the group consisting of: trihexyphenidyl, biperidin and hyoscyamine~~

~~6. The POZ conjugate of claim 2, wherein the monamine oxidase-B inhibitor is selected from the group consisting of: seligiline and rasagiline.~~

~~7. The POZ conjugate of claim 2, wherein the COMT inhibitor is selected from the group consisting of: tolcapone and entacapone.~~

~~8. The POZ conjugate of claim 2, wherein the adenosine A_{2A} receptor antagonist is selected from the group consisting of: preladenant, theophylline and istradefylline.~~

~~9. The POZ conjugate of claim 2, wherein the GABA-uptake inhibitor is selected from the group consisting of: tiagabine and nipecotic acid.~~

5~~10~~. The POZ conjugate of any one of claims 2 to 4 ~~9~~, wherein the release rate of the agent from the POZ conjugate is controlled by selecting the POZ polymer characteristic, wherein the POZ polymer characteristic is selecting a pendent moiety containing a hydrophilic or a hydrophobic portion, selecting a pendant group on the POZ polymer portion with a hydrophobic character, selecting a selected molecular weight for the POZ polymer portion, or a combination of the foregoing.

~~11~~6. The POZ conjugate of any one of claims 2 to 4 ~~9~~, wherein the release rate of the agent from the POZ conjugate is controlled by selecting the loading characteristic, wherein the loading characteristic is selecting a loading percentage of the agent.

~~12~~7. The POZ conjugate of any one of claims 2 to 4 ~~9~~, wherein the release rate of the agent from the POZ conjugate is controlled by selecting the agent characteristic, wherein the agent characteristic is selecting an agent with a selected solubility in water, selecting an agent with a selected molecular volume, selecting an agent with a selected total polar surface area, or a combination of the foregoing.

~~13. The POZ conjugate of claim 1, wherein the agent is a phytocannabinoid and the POZ conjugate comprises a loading percentage of the phytocannabinoid from 1.6% ± 1% to 9.6% ± 1% (w/w phytocannabinoid to POZ polymer), and the release rate of the phytocannabinoid from the POZ conjugate is controlled by the loading percentage.~~

~~14. The POZ conjugate of claim 13 further comprising a pendent moiety containing a hydrophilic or a hydrophobic portion linked to the POZ polymer and the release rate ofthe phytocannabinoid from the POZ conjugate is controlled by the loading percentage and the hydrophilic or the hydrophobic portion.~~

~~15. The POZ conjugate of claim 13, wherein the pendent moiety containing a hydrophilic or a hydrophobic portion is linked to the POZ polymer by a non-degradable linkage.~~

~~16~~8. The POZ conjugate o~~f claim 1~~ any one of claims 1-4 or 5-7, or a pharmaceutically acceptable salt thereof, having the structure

$$R\text{-}\{[N(CO\text{-}L_1\text{-}R_1)CH_2CH_2]_m\text{-}[N(COR_2\text{-}A)CH_2CH_2]o\text{-}[N(COX)CH_2CH_2]_n\}_a\text{-}T$$

A is the agent;
R is ~~an initiating group~~ hydrogen, unsubstituted alkyl or substituted alkyl;
R_1 is a pendent moiety containing a hydrophilic or a hydrophobic portion;
L_1 is a linking group linking R_1 to the POZ polymer or is absent;
R_2 is a pendent moiety comprising the physiologically degradable linkage linking the POZ polymer and A;
X is a ~~pendent~~ pendant group;

T is a terminating group;

a is ran ~~which~~ that indicates a random copolymer or block ~~which~~ that indicates a block copolymer;

m is an integer from 0 to 100;

n is an integer from 0 to 1000, provided that if m is 0, the n is an integer from 1 to 1000; and

o is an integer from 1 to 50.

~~17. The POZ conjugate of claim 16, wherein R is hydrogen, unsubstituted alkyl or substituted alkyl.~~

~~18. The POZ conjugate of claim 16, wherein X is independently selected for each repeating unit from an unsubstituted or substituted alkyl, an unsubstituted or substituted alkenyl, an unsubstituted or substituted aralkyl or an unsubstituted or substituted heterocyclylalkyl group.~~

~~19. The POZ conjugate of claim 16, wherein X is independently selected for each repeating unit from an unsubstituted alkyl.~~

~~20. The POZ conjugate of claim 16, wherein T is a thioalkyl carboxylic acid, a thiocarboxylic ester, or a hydroxyl.~~

~~21. The POZ conjugate of claim 16, wherein T is Z-B-Q, wherein Z is S, 0, or N, B is an optional linking group, and Q is a terminating nucleophile or a terminating portion of a nucleophile.~~

~~22. The POZ conjugate of claim 21, wherein B is -(CH2)y- and y is an integer selected from 1 to 16.~~

~~23. The POZ conjugate of claim 21, wherein Q is an alkyne, alkene, amine, oxyamine, aldehyde, ketone, acetal, thiol, ketal, maleimide, ester, carboxylic acid, activated carboxylic acid, an active carbonate, a chloroformate, alcohol, azide, vinyl sulfone, orthopyridyl disulfide or an inert group.~~

~~24. The POZ conjugate of claim 21, wherein T is -S-CH2CH2-CO2CH3, -S-CH2CH2-CO2H), -S-CH2CH2-NH2, or, -S-CH2CH2-NH-tBoc.~~

~~25~~9. The POZ conjugate of claim ~~16~~8, wherein m is from 1 to 100 and the release rate of the agent from the POZ conjugate is controlled by the loading percentage and R_1.

~~26. The POZ conjugate of claim 25, wherein Ri is Li-Ri and Li is a non-degradable linkage.~~

~~27. The POZ conjugate of claim 26, wherein Ri contains the hydrophilic portion.~~

~~28. The POZ conjugate of claim 27, wherein Ri contains one or more polar covalent bonds.~~

~~29. The POZ conjugate of claim 27, wherein Ri is independently selected for each repeating unit from a water soluble polymer, a substituted alkyl, a substituted alkenyl, a substituted alkynyl, a substituted aralkyl, or a substituted heterocyclylalkyl group.~~

~~30. The POZ conjugate of claim 29, wherein the substituted alkyl, the substituted alkenyl, them substituted alkynyl, the substituted aralkyl, the substituted heterocyclylalkyl group, or a combination of the foregoing, contain one or more oxygen atoms, nitrogen atoms, sulfur atoms, phosphorous atoms, or a combination of the foregoing.~~

~~31. The POZ conjugate of claim 29, wherein the water soluble polymer is a poly(alkylene glycol), a copolymer of poly(alkylene glycol), a poly(oxyethylated polyol), a poly(olefinic alcohol), a poly(vinylpyrrolidone), a poly(hydroxyalkylmethacrylamide), a poly(hydroxyalkylmethacrylate), a poly(saccharides), a poly(a-hydroxy acid), a poly(vinyl alcohol), a polyphosphazene, a polyoxazoline, a poly(N-acryloylmorpholine), or a combination of any of the foregoing.~~

~~32. The POZ conjugate of claim 31, wherein the water soluble polymer contains from 1 to 30 repeating units.~~

~~33. The POZ conjugate of claim 27, wherein Ri is independently selected for each repeating unit from a Cl to C5 alcohol, a Cl to C5 carboxylic acid, or a poly(alkylene glycol) containing from 2 to 10 repeating units.~~

~~34. The POZ conjugate of claim 27, wherein at least one hydrophilic portion of Ri is located within 50 angstroms from the N group to which Ri is linked.~~

~~35. The POZ conjugate of claim 26, wherein Ri contains the hydrophobic portion.~~

~~36. The POZ conjugate of claim 35, wherein at least one hydrophobic portion of Ri is located within 50 angstroms from the N group to which Ri is linked.~~

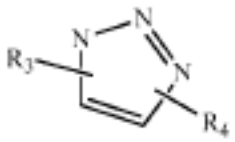
~~37. The POZ conjugate of claim 16, wherein R_2 is L_2.~~

~~38~~10. The POZ conjugate of claim ~~37~~ 8, wherein the physiologically degradable linkage comprises a cleavable moiety selected from the group consisting of: esters, carboxylate esters, carbonate esters, carbamates, amides, disulfides, and peptides.

~~39~~11. The POZ conjugate of any one of claims 8 or 10 ~~claim 37~~, wherein ~~L~~is non-degradable linkage, L_2 is a linking group containing the physiologically degradable linkage, wherein T is Z-B-Q, and wherein Z is S, B is -(CH_2)y-, y is an integer from 1-3, and Q is -COOCH3, -COOH, or -NH2.

~~40. The POZ conjugate of claim 37, wherein Li and L_2 are each independently a di-substituted triazole.~~

~~41. The POZ conjugate of claim 40, wherein for L_2 the disubstituted triazole has the structure:~~



wherein:

R_3 is a linker linking the triazole moiety to the POZ polymer; and

R_4 is a linker linking the triazole moiety to the agent.

42. The POZ conjugate of claim 41, wherein R_3 is $-C(0)-R_5-$, wherein R_5 is absent or is an unsubstituted or substituted alkyl, an unsubstituted or substituted alkenyl, an unsubstituted or substituted aralkyl, or an unsubstituted or substituted heterocyclylalkyl group.

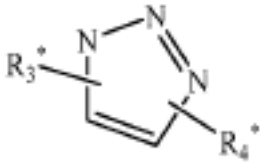
43. The POZ conjugate of claim 42, wherein R5 is absent or is a unsubstituted alkyl from 1 to 10 carbons in length.

44. The POZ conjugate of claim 41, wherein R_4 is $-R_6-R_7-R_8-$, R_6 is a substituted or unsubstituted alkyl, substituted or unsubstituted aralkyl or $-(CH2CH2O)e-$, e is an integer from 1-10, R_7 is a group comprising a cleavable moiety or a portion of the cleavable moiety, and R_8 is absent or 0.

45. The POZ conjugate of claim 44, wherein R_6 is a straight chain substituted or unsubstituted Cl-C10 alkyl or a branched substituted or unsubstituted C1-C10 alkyl, R_7 is $-C(0)-$ and R_8 is $-O-$ or R_6 is a straight chain substituted or unsubstituted Cl-C10 alkyl or a branched substituted or unsubstituted Cl-C10 alkyl, R_7 is $-C(0)-O-$ and R_8 is absent.

46. The POZ conjugate of claim 41, wherein for R_3 is $-C(0)-(CH_2)_3-$ and R_4 is independently selected for each repeating unit from $-(CH_2)d-C(0)-$, $-CH_2-C(0)-$, $-CH_2-CH_2-C(0)-$, $-CH_2-CH_2-CH_2-C(0)-$, $-CH_2(CH_3)-C(0)-$, $-(CH_2)d-C(0)-O-$, $-CH_2-C(0)-O-$, $-CH_2-CH_2-C(0)-O-$, $-CH_2-CH_2-CH_2-C(0)-O-$, or $-CH_2(CH_3)-C(0)-O-$, wherein d is an integer from 1 to 10.

47. The POZ conjugate of claim 40, wherein for Li the disubstituted triazole has the structure:



wherein:

R_3* is a linker linking the triazole moiety to the POZ polymer; and

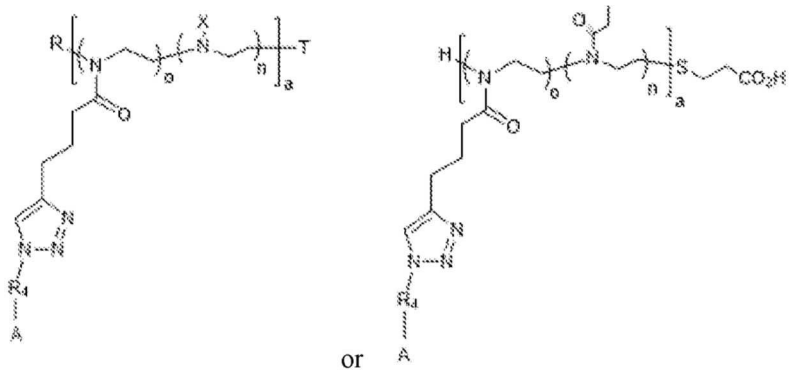
R_4* is a linker linking the triazole moiety to R_1 or R_4 is R_1.

48. The POZ conjugate of claim 47, wherein R_3* is $-C(0)-R_5-$, wherein R_5 is absent or is an unsubstituted or substituted alkyl, an unsubstituted or substituted alkenyl, an unsubstituted or substituted aralkyl, or an unsubstituted or substituted heterocyclylalkyl group.

~~49. The POZ conjugate of claim 49, wherein R5 is absent or is a unsubstituted alkyl from 1 to 10 carbons in length~~

~~50. The POZ conjugate of claim 47, wherein R_3* is -C(0)-$(CH_2)_3$- and R_4* is independently selected for each repeating unit from a C1 to C5 alcohol, a C1 to C5 carboxylic acid, or a poly(alkylene glycol) containing from 2 to 10 repeating units.~~

~~51~~12. The POZ conjugate of claim 16 having the structure:



or

wherein

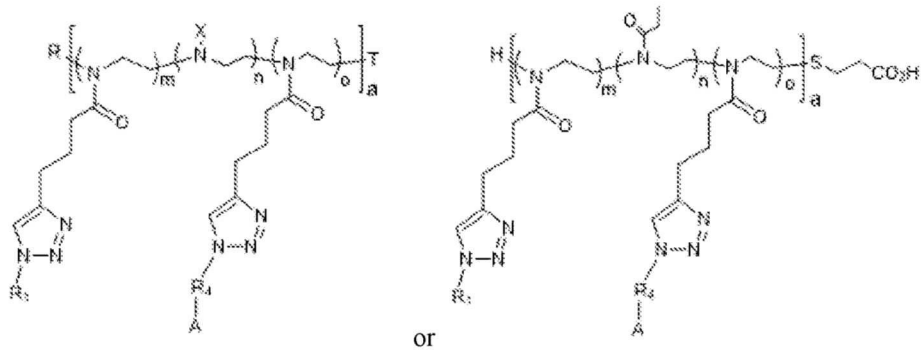
R_4 is independently selected for each repeating unit from -$(CH_2)_d$-C(O)-, -CH_2-C(O)-, -CH_2-CH_2-C(O)-, -CH_2-CH_2-CH_2-C(O)-, -$CH_2(CH_3)$-C(O)-, -$(CH_2)_d$-C(O)-O-, -CH_2-C(O)-O-, -CH_2-CH_2-C(O)-O-, -CH_2-CH_2-CH_2-C(O)-O-, or -$CH_2(CH_3)$-C(O)-O-;

d is an integer from 1 to 10; and

the release rate of the agent from the POZ conjugate is controlled by the loading percentage.

~~52~~. ~~The POZ of 51, wherein R_4 is -CH_2-C(0), -CH_2-CH_2-C(0)-, or -$CH_2(CH_3)$-C(0) and m and n are each an integer independently selected from 2-8.~~

~~53~~13. The POZ conjugate of claim ~~16~~8 having the structure:



or

wherein:

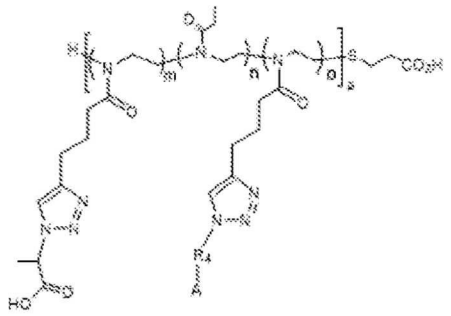
R_1 is independently selected for each repeating unit from a water soluble polymer, a substituted alkyl, a substituted alkenyl, a substituted alkynyl, a substituted aralkyl, or a substituted heterocyclylalkyl group;

R_4 is independently selected for each repeating unit from $-(CH_2)_d-C(O)-$, $-CH_2-C(O)-$, $-CH_2-CH_2-C(O)-$, $-CH_2-CH_2-CH_2-C(O)-$, $-CH_2(CH_3)-C(O)-$, $-(CH_2)_d-C(O)-O-$, $-CH_2-C(O)-O-$, $-CH_2-CH_2-C(O)-O-$, $-CH_2-CH_2-CH_2-C(O)-O-$, or $-CH_2(CH_3)-C(O)-O-$; d is an integer from 1 to 10; and the release rate of the agent from the POZ conjugate is controlled by the loading percentage and the R_1.

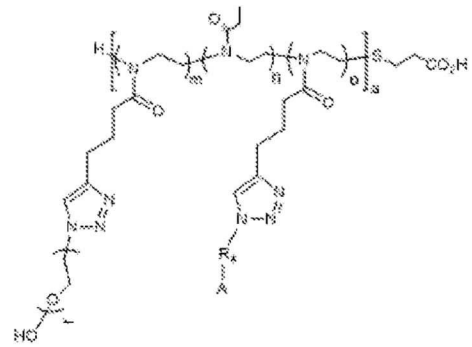
~~54. The POZ of 53, wherein R_4 is $-CH_2-C(0)$, $-CH_2-CH_2-C(0)$, or $-CH_2(CH_3)-C(0)$ and m and n are each an integer independently selected from 2-8.~~

~~55. The POZ conjugate of claim 53, wherein R_4 is independently selected for each repeating unit from a Cl to C5 alcohol, a Cl to C5 carboxylic acid, or a poly(alkylene glycol) containing from 2 to 10 repeating units.~~

~~56~~14. The POZ conjugate of claim ~~16~~8 having the structure:



or



wherein:

f is an integer from 1-10;

R_4 is independently selected for each repeating unit from -$(CH_2)_d$-C(O)-, -CH_2-C(O)-, -CH_2-CH_2-C(O)-, -CH_2-CH_2-CH_2-C(O)-, -$CH_2(CH_3)$-C(O)-, -$(CH_2)_d$-C(O)-O-, -CH_2-C(O)-O-, -CH_2-CH_2-C(O)-O-, -CH_2-CH_2-CH_2-C(O)-O-, or -$CH_2(CH_3)$-C(O)-O-; d is an integer from 1 to 10; and the release rate of the agent from the POZ conjugate is controlled by the loading percentage and the hydrophilic portion.

~~57. The POZ of 56, wherein R_4 is -CH_2-C(0), -CH_2-CH_2-C(0) , or -$CH_2(CH_3)$-C(0) and m and n are each an integer independently selected from 2-8.~~

~~58. The POZ conjugate of anyone of claims 16 to 57, wherein the agent is a phytocannabinoid, a dopamine agonist, an anticholinergic, a monamine oxidase-B inhibitor, a catechol-O-methyl transferase (COMT) inhibitor or an adenosine A_{2A} receptor antagonist, or a GABA-uptake inhibitor.~~

~~59. The POZ conjugate of claim 58, wherein the phytocannabinoid is selected from the group consisting of: cannabidiol, cannabigerol, cannabigerolic acid, cannabidiolic acid, cannabidiolmonomethylether, cannabidiol-C4, cannabidarinic acid, cannabidivarin, cannabidiol or cannabigerol propyl variant, cannabichromene, cannabichromenic acid, cannabichromevarinic acid, cannabichromevarin, cannabinol, cannabicyclol, tetrahydrocannabivarin, A9-THC, ajulemic acid, and dexanabinol.~~

~~60. The POZ conjugate of claim 58, wherein the dopamine agonist is selected from the group consisting of: apomorphine, arbutamine, carbidopa, dobutamine, dopamine, entacapone, epinephrine, fenoldopam, isoetharine, isoproterenol, levopoda, levonordefrin, masaprocol, methyldopa, methyldopate, norepinephrine, protokylol, tolcapone, or (r) (+) fenoldopam, rotigotine, pramipexole, quinagolide, 5-OH DPAT, ropinirole, pergolide, cabergoline, or bromocriptine.~~

~~61. The POZ conjugate of claim 58, wherein the anticholinergic is selected from the group consisting of: trihexyphenidyl, biperidin and hyoscyamine~~

~~62. The POZ conjugate of claim 58, wherein the monamine oxidase-B inhibitor is selected from the group consisting of: seligiline and rasagiline.~~

~~63. The POZ conjugate of anyone of claim 58, wherein the COMT inhibitor is selected from the group consisting of: tolcapone and entacapone.~~

~~64. The POZ conjugate of anyone of claim 58, wherein the adenosine A2A receptor antagonist is selected from the group consisting of: preladenant, theophylline and istradefylline.~~

~~65. The POZ conjugate of anyone of claim 58, wherein the GABA-uptake inhibitor is selected from the group consisting of: tiagabine and nipecotic acid.~~

66. The POZ conjugate of any one of claims 16 to 57, wherein the phytocannabinoid is cannabidiol (CBD) and the POZ conjugate contains 1.6% ± 1% CBD (w/w CBD to POZ polymer).

67. The POZ conjugate of any one of claims 16 to 57, wherein the phytocannabinoid is cannabidiol and the POZ conjugate contains 3.6% + 1% CBD (w/w CBD to POZ polymer).

68. The POZ conjugate of any one of claims 16 to 57, wherein the phytocannabinoid is cannabidiol and the POZ conjugate contains 5.6% ± 1% CBD (w/w CBD to POZ polymer).

69. The POZ conjugate of any one of claims 16 to 57, wherein the phytocannabinoid is cannabidiol and the POZ conjugate contains 7.6% ± 1% CBD (w/w CBD to POZ polymer).

70. The POZ conjugate of any one of claims 16 to 57, wherein the phytocannabinoid is cannabidiol and the POZ conjugate contains 9.6% ± 1% CBD (w/w CBD to POZ polymer).

71. A method of treating a disorder benefiting from agonism or antagonism of a CB1 receptor, CB2 receptor, 5H1-a receptor, 5H2-a receptor, TRP-V1 receptor, TRP-V2 receptor, TRP-V3 receptor, adenosine A2A receptor, GPR55 receptor, PPAR-a, PPAR-y receptor, or a combination of the foregoing in a subject, the method comprising administering to the subject a single dose of a composition comprising a POZ conjugate according to a dosing interval for a treatment period, the POZ conjugate comprising a water-solupolyoxazoline (POZ) polymer, a phytocannabinoid linked to the POZ polymer by a physiologically degradable linkage, and an optional pendent moiety linked to the POZ polymer containing a hydrophilic or a hydrophobic portion, or a pharmaceutically acceptable form thereof, wherein the POZ conjugate contains 0.25 mg eq/kg to 5 mg eq/kg of the phytocannabinoid.

72. The method of claim 71, wherein the phytocannabinoid is selected from the group consisting of: cannabidiol, cannabigerol, cannabigerolic acid, cannabidiolic acid, cannabidiolmonomethylether, cannabidiol-C4, cannabidarinic acid, cannabidivarin, cannabidiol or cannabigerol propyl variant, cannabichromene, cannabichromenic acid, cannabichromevarinic acid, cannabichromevarin, cannabinol, cannabicyclol, tetrahydrocannabivarin, A9-THC, ajulemic acid, and dexanabinol.

73. The method of claim 72, wherein the phytocannabinoid is cannabidiol (CBD).

74. The method of claim 73, wherein the POZ conjugate contains 1.6% ± 1.0% to 9.6% ± 1.0% CBD (w/w CBD to POZ polymer).

75. The method of claim 73, wherein the single dose of a POZ conjugate contains between 0.25 mg eq/kg to 2.5 mg eq/kg of CBD.

76. The method of claim 75, wherein a plasma concentration of CBD in the subject is greater than a minimum therapeutic level during all or substantially all of the dosing interval or the treatment period.

77. The method of claim 76, wherein the dosing interval is two times per week, one time per week, one time every two weeks or 1 time every 4 weeks.

78. The method of claim 77, wherein the minimum therapeutic level is 5 ng/ml.

79. The method of claim 77, wherein the minimum therapeutic level is 50 ng/ml.

80. The method of claim 77, wherein the minimum therapeutic level is 150 ng/ml.

81. The method of claim 77, wherein the minimum therapeutic level is 500 ng/ml.

82. The method of claim 77, wherein the minimum therapeutic level is 1000 ng/ml.

83. The method of claim 76, wherein the treatment period is 7 days to 60 months.

84. The method of claim 76, wherein the treatment period is continuous.

85. The method of claim 73, wherein the single dose of a POZ conjugate contains between 2.5 mg eq/kg to 5.0 mg eq/kg of CBD.

86. The method of claim 85, wherein a plasma concentration of CBD is greater than a minimum therapeutic level during all or substantially all of the dosing interval.

87. The method of claim 86, wherein the dosing interval is two times per week, one time per week, one time every two weeks or 1 time every 4 weeks.

88. The method of claim 87, wherein the minimum therapeutic level is 5 ng/ml.

89. The method of claim 87, wherein the minimum therapeutic level is 50 ng/ml.

90. The method of claim 87, wherein the minimum therapeutic level is 150 ng/ml.

91. The method of claim 87, wherein the minimum therapeutic level is 500 ng/ml.

92. The method of claim 87, wherein the minimum therapeutic level is 1000 ng/ml.

93. The method of claim 87, wherein the minimum therapeutic level is 1500 ng/ml.

94. The method of claim 86, wherein the treatment period is 7 days to 60 months.

95. The method of claim 86, wherein the treatment period is continuous.

96. The method of any one of claims 71 to 95, wherein the disease or condition is selected from the group consisting of: pain, acute pain, chronic pain, neuropathic pain, cancer pain, neurodegenerative disease, post-traumatic stress disorder, agitation associated with dementia, insomnia, REM sleep behavior disorder, excessive daytime sleepiness,

nightmares associated with posttraumatic stress disorder, obstructive sleep apnea, essential tremor, Tourette syndrome, depression, fibromyalgia, ischemic disease, stroke, cardiac ischemia, coronary artery disease, thromboembolism, myocardial infarction, brain injury, traumatic brain injury, diffuse axonal injury, concussion, contusion, anoxic brain injury, hypoxic brain injury, age related inflammatory disease, age related autoimmune disease, cachexia, AIDS wasting disease, weight loss associated with cancer, weight loss associated with chronic obstructive pulmonary disease, weight loss associated with infectious disease, nausea, vomiting, glaucoma, movement disorders, rheumatoid arthritis, asthma, allergy, psoriasis, Crohn's disease, systemic lupus erythematosus, diabetes, cancer, osteoporosis, renal ischemia, and nephritis.

97. The method of claim 96, wherein the neurodegenerative disease is selected from the group consisting of: Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, multiple sclerosis, multiple sclerosis ataxia/spasticity syndrome, dystonia associated with Parkinson's disease, dystonia associated with Huntington's disease, frontotemporal dementia, prion disease, Lewy body dementia, motor neuron disease, spinomuscular atrophy, spinocerebellar ataxia, progressive supranuclear palsy, Fragile X-associated tremor/ataxia syndrome, Fragile X-associated behavioral abnormalities, autism spectrum disorder, vascular dementia, normal pressure hydrocephalus, traumatic spinal cord injury, HIV dementia, alcohol induced neurotoxicity, Down's syndrome, epilepsy, partial seizures, generalized seizures, tonic-clonic seizures, absence seizures, atonic seizures, treatment-resistant epilepsy, Lennox-Gastaut syndrome, Dravet syndrome, Ohtahara syndrome, West syndrome, Doose syndrome, CDKLS encephalopathy, Landau-Kleffner syndrome, hypoxic-ischemic encephalopathy, early myoclonic epilepsy, Rhett's syndrome, and febrile infection related epilepsy syndrome.

98. A method of achieving a plasma concentration of a phytocannabinoid above a minimum therapeutic level in a subject for all or substantially all of a dosing interval or a treatment period, the method comprising administering to the subject over the dosing interval a single dose of a POZ conjugate comprising a water-soluble polyoxazoline (POZ) polymer, the phytocannabinoid linked to the POZ polymer by a physiologically degradable linkage, and an optional pendent moiety linked to the POZ polymer containing a hydrophilic or a hydrophobic portion, or a pharmaceutically acceptable form thereof, wherein the POZ conjugate contains 0.25 mg eq/kg to 5 mg eq/kg of the phytocannabinoid.

99. The method of claim 98, wherein the phytocannabinoid is selected from the group consisting of: cannabidiol, cannabigerol, cannabigerolic acid, cannabidiolic acid, cannabidiolmonomethylether, cannabidiol-C4, cannabidarinic acid, cannabidivarin, cannabidiol or cannabigerol propyl variant, cannabichromene, cannabichromenic acid, cannabichromevarinic acid, cannabichromevarin, cannabinol, cannabicyclol, tetrahydrocannabivarin, Δ9-THC, ajulemic acid, and dexanabinol.

100. The method of claim 98, wherein the phytocannabinoid is cannabidiol (CBD).

101. The method of claim 100, wherein the POZ conjugate contains 1.6% ± 1.0% to 9.6% ±1.0% CBD (w/w CBD to POZ polymer).

102. The method of claim 100, wherein the single dose of a POZ conjugate contains between 0.25 mg eq/kg to 2.5 mg eq/kg of CBD.

103. The method of claim 102, wherein a plasma concentration of CBD in the subject is greater than a minimum therapeutic level during all or substantially all of the dosing interval orthe treatment period.

104. The method of claim 103, wherein the dosing interval is two times per week, one time per week, one time every two weeks or 1 time every 4 weeks.

105. The method of claim 104, wherein the minimum therapeutic level is 5 ng/ml.

106. The method of claim 104, wherein the minimum therapeutic level is 50 ng/ml.

107. The method of claim 104, wherein the minimum therapeutic level is 150 ng/ml.

108. The method of claim 104, wherein the minimum therapeutic level is 500 ng/ml.

109. The method of claim 104, wherein the minimum therapeutic level is 1000 ng/ml.

110. The method of claim 103, wherein the treatment period is 7 days to 60 months.

111. The method of claim 103, wherein the treatment period is continuous.

112. The method of claim 100, wherein the single dose of a POZ conjugate contains between 25 2.5 mg eq/kg to 5.0 mg eq/kg of CBD.

113. The method of claim 112, wherein a plasma concentration of CBD is greater than a minimum therapeutic level during all or substantially all of the dosing interval.

114. The method of claim 113, wherein the dosing interval is two times per week, one time per week, one time every two weeks or 1 time every 4 weeks.

115. The method of claim 114, wherein the minimum therapeutic level is 5 ng/ml.

116. The method of claim 114, wherein the minimum therapeutic level is 50 ng/ml.

117. The method of claim 114, wherein the minimum therapeutic level is 150 ng/ml.

118. The method of claim 114, wherein the minimum therapeutic level is 500 ng/ml.

119. The method of claim 114, wherein the minimum therapeutic level is 1000 ng/ml.

~~120. The method of claim 114, wherein the minimum therapeutic level is 1500 ng/ml.~~

~~121. The method of claim 113, wherein the treatment period is 7 days to 60 months.~~

~~122. The method of claim 113, wherein the treatment period is continuous.~~

15. A polyoxazoline (POZ) conjugate comprising a water-soluble POZ polymer and a phytocannabinoid linked to the water-soluble POZ polymer by a physiologically degradable linkage, or a pharmaceutically acceptable form thereof, wherein the POZ conjugate comprises a loading percentage of the phytocannabinoid from 1.6% ± 1% to 9.6% ± 1% (w/w phytocannabinoid to POZ polymer), and wherein a release rate of the phytocannabinoid from the POZ conjugate is controlled by the loading percentage.

16. The POZ conjugate of claim 123 further comprising a pendent moiety containing a hydrophilic or a hydrophobic portion linked to the POZ polymer and the release rate of the phytocannabinoid from the POZ conjugate is controlled by the loading percentage and the hydrophilic or the hydrophobic portion.

17. The POZ conjugate of claim 123, wherein the pendent moiety containing a hydrophilic or a hydrophobic portion is linked to the POZ polymer by a non-degradable linkage.

18. The POZ conjugate of claim 123, or a pharmaceutically acceptable salt thereof, having the structure

$$R\text{-}\{[N(CO\text{-}L_1\text{-}R_1)CH_2CH_2]_m\text{-}[N(COR_2\text{-}A)CH_2CH_2]o\text{-}[N(COX)CH_2CH_2]_n\}_a\text{-}T$$

A is the agent;

R is hydrogen, unsubstituted alkyl or substituted alkyl;

R_1 is a pendent moiety containing a hydrophilic or a hydrophobic portion;

L_1 is a linking group linking R_1 to the POZ polymer or is absent;

R_2 is a pendent moiety comprising the physiologically degradable linkage linking the POZ polymer and A;

X is a pendant group;

T is a terminating group;

a is ran that indicates a random copolymer or block that indicates a block copolymer;

m is an integer from 0 to 100;

n is an integer from 0 to 1000, provided that if m is 0, the n is an integer from 1 to 1000; and

o is an integer from 1 to 50.