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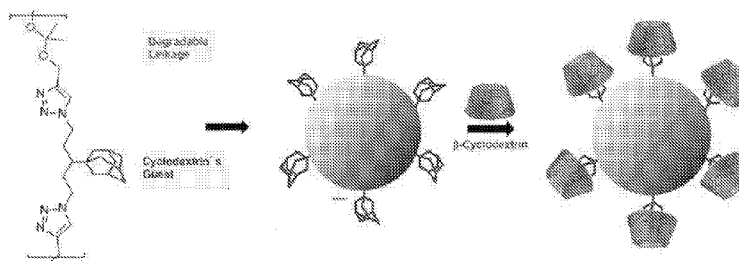


Figure 8

(57) Abstract: The present disclosure is in the field of biomedical, pharmaceutical and polymeric sciences. The present disclosure relates to the conjugates of pendant polymers capable of forming guest:host complexes or covalent/non-covalent conjugates with cyclodextrins (or their derivatives), corresponding method of preparation and their application in treating lipid storage disorders. These conjugates possess improved properties including but not limiting to prolonged duration of action in cell and increased efficacy in removal of cholesterol from cells.

WO 2017/006279 A1

**“CYCLODEXTRIN-POLYMER COMPLEXES AND COMPOSTIONS
AND METHODS OF MAKING AND USING THE SAME”**

PRIORITY INFORMATION

5 [0001] This application claims the benefit of Indian Provisional Patent Application No. 3505/CHE/2015, filed on July 8, 2015, which is incorporated herein by reference in its entirety for all purposes.

TECHNICAL FIELD

10 [0002] The present disclosure is in the field of biomedical, pharmaceutical and polymeric sciences, including the synthesis of a macromolecular therapeutic agents and processes for preparing such agents. In particular, the disclosure relates to conjugates of pendant polymers capable of forming guest:host complexes with cyclodextrins or cyclodextrin derivatives, method of preparing such conjugates,
15 and the use of such conjugates in the treatment of diseases including lipid storage disorders. The present conjugates possess improved properties including but not limiting to prolonged duration of action in cells and increased efficacy in removal of lipids (e.g., cholesterol) from cells.

20 **BACKGROUND**

[0003] Lipid storage diseases, or the lipidoses, are a group of inherited metabolic disorders in which harmful amounts of lipids accumulate in various cells and tissues in the body. People with these disorders typically exhibit an elevated level of cholesterol in tissues of the body, since these people either do not produce
25 adequate quantities of one or more enzymes needed to metabolize lipids, or they produce enzymes that do not function properly to remove lipids. In recent years, sedentary lifestyles and poor diet habits have also become factors leading to lipid storage disorders.

30 [0004] Niemann-Pick type C disorder (NPC) is a lysosomal storage disorder caused by accumulation of unesterified cholesterol and sphingolipids in the lysosomes of brain, liver, spleen, and lung cells. Aberrant accumulation of

cholesterol in NPC cells has been shown to originate from mutation of genes encoding either the membrane-bound NPC1 proteins or the soluble NPC2 proteins required for cholesterol efflux from the lysosome. Unfortunately, the treatment options are limited for this typically fatal disease.

5

No significant therapeutic benefit has been achieved by reducing cholesterol storage by treating with dietary reduction or knock-out of Low Density lipoprotein receptors. There has been intensive research aimed at identifying a reliable cure or preventive measures for lipid storage disorders including NPC.

10 Chaperone-based therapy, gene therapy and recombinant enzyme therapies are some of the important therapeutic regimens attempted in this area for treating lipid storage disorders including Niemann-Pick Type C disorder, which are still in various stages of development. Furthermore, some benefit has been reported in a clinical trial using Miglustat (OGT 918, N-butyl-deoxyojirimycin) but currently
15 no clinically approved cure exists for lipid storage disorders, especially Niemann-Pick Type C disorder.

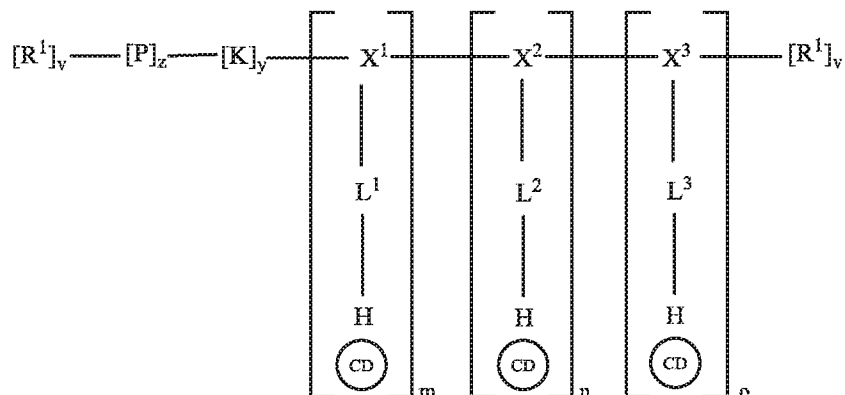
[0005] Hydrophilic molecules, such as cyclodextrin, which are generally employed to treat lipid storage disorders undergo rapid clearance from the
20 bloodstream due to their high water solubility. Therefore, to maintain a minimum effective concentration of a therapeutic drug, usually high concentrations/doses or repeated administration of these hydrophilic drugs are required to be administered to the subject. Administration of higher concentrations/doses of any therapeutic agent/drug to the subject may lead to toxicity and adverse effects to various
25 organs of the subject. Thus, hydrophilic therapeutic agents suffer drawbacks stemming from rapid clearance from the body. Hence, to bring a striking balance between the clearance rate of hydrophilic therapeutic agents and maintaining minimum effective concentration of these drugs in the desired site of organ without compromising the efficacy of the drug, is a critical objective in the
30 research and development of drug discovery and drug delivery systems.

[0006] Accordingly, there has been a continuing need in the art to provide drugs/drug-polymer complexes having improved/greater efficacy along with prolonged duration of action for treating lysosomal lipid storage disorders including NPC. The present disclosure aims at overcoming the aforesaid drawbacks of the prior art.

[0007] Accordingly, there has been a continuing need in the art to provide drugs/drug-polymer complexes having improved/greater efficacy along with prolonged duration of action for treating lysosomal lipid storage disorders including NPC. The present disclosure aims at overcoming the aforesaid drawbacks of the prior art.

STATEMENT OF THE DISCLOSURE

[0008] The present disclosure provides a compound comprising the following structure:



wherein

R^1 is independently 2-hydroxy propyl, 1-hydroxy methyl, OH, CO_2H or NH_2 ;

P is a polymer;

X^1 , X^2 and X^3 are each backbone moieties;

L^1 , L^2 , L^3 and K are each linker moieties, wherein each of L^1 , L^2 and L^3 may be present or absent, provided at least one of L^1 , L^2 and L^3 is present;

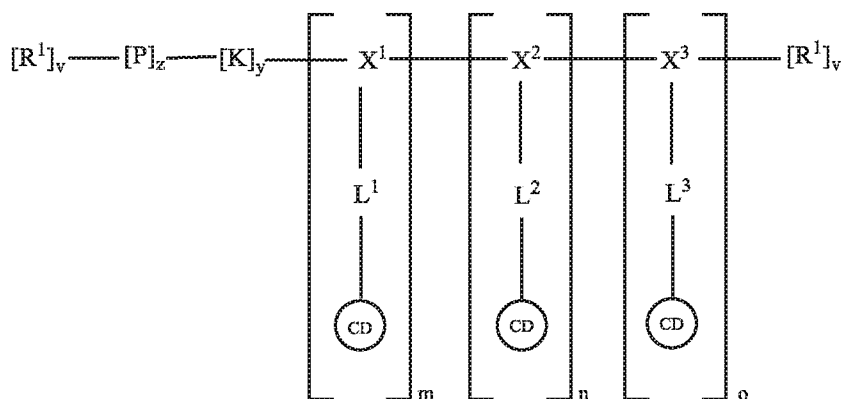
H is host moiety attached directly to the backbone moiety or via the linker moiety;

- 5 CD is a cyclodextrin, or a derivative thereof; wherein CD is non-covalently conjugated to H ;

m , n and o are each independently from 0 to 1000, wherein at least one of m , n and o is at least 4; and

v , z and y are each independently 0 to 500.

- 10 [0009] The present disclosure provides a compound comprising the following structure:



wherein

- 15 R^1 is independently 2-hydroxy propyl, 1-hydroxy methyl, OH, CO_2H or NH_2 ;

P is a polymer;

X^1 , X^2 and X^3 are each backbone moieties;

L^1 , L^2 , L^3 and K are each linker moieties, wherein each of L^1 , L^2 and L^3 may be present or absent, provided at least one of L^1 , L^2 and L^3 is present;

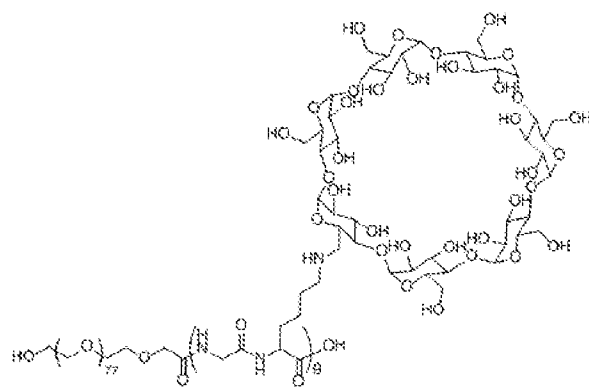
CD is a cyclodextrin, or a derivative thereof, wherein each CD is covalently attached to respective L^1 , L^2 , L^3 ; and

5 m, n and o are each independently from 0 to 1000, wherein at least one of m, n and o is at least 4; and

v, z and y are each independently 0 to 500.

[0010] The present disclosure provides a compound selected from:

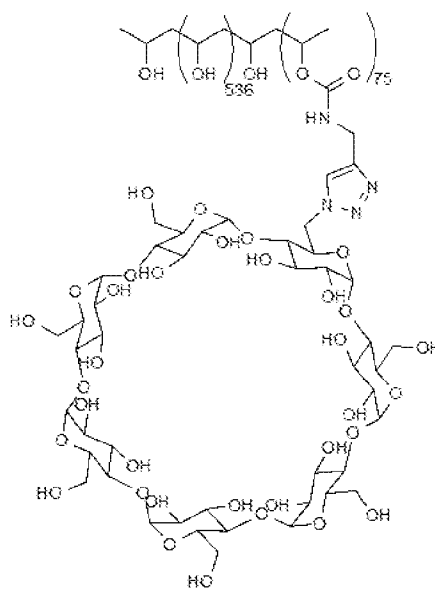
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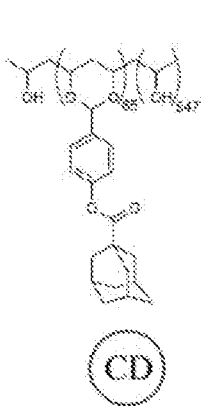
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PEG-[Glycine-(Lysine- β -CD)]₉

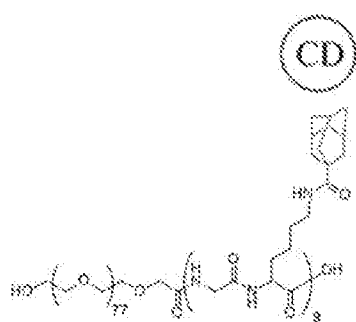
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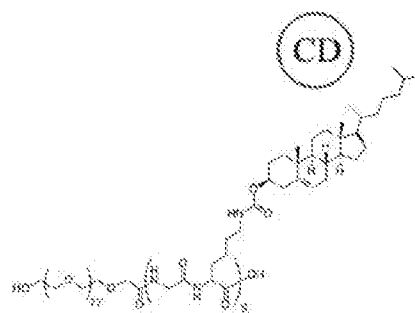
Poly(vinyl alcohol)-trz-(β -CD)₇₅



**Poly(vinyl alcohol)-
(Adamantane)₆₅
complexed with CD**

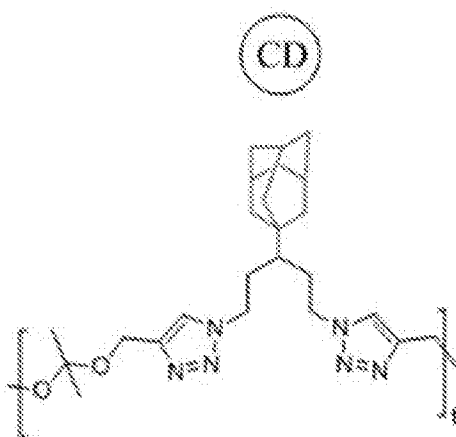


**PEG-[Glycine-(Lysine-
Adamantane)]₉
complexed with CD**



**PEG-[Glycine-(Lysine-
Cholesterol)]₉
complexed with CD**

5



wherein 't' ranges from 5 to 500

**pADK polymer
complexed with CD**

10 [0011] The present disclosure provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier or a pharmaceutical excipient and a compound as described herein.

[0012] The pharmaceutical composition can further comprising a therapeutically active agent.

[0013] The present disclosure provides a method of treating a disease or a condition associated with abnormal NPC1 and/or NPC2 protein production, comprising administering to a subject in need thereof a compound or a composition as described herein.

- 5 [0014] The present disclosure provides a method of treating lipid storage disorder comprising administering to a subject in need thereof a compound or a composition as described herein.

[0015] The present disclosure provides a method of treating Niemann-Pick disease, comprising administering to a subject in need thereof a compound or a
10 composition as described herein.

[0016] The present disclosure provides a compound as described herein where the compound has an elimination half-life of from about 6 hours to about 24 hours.

[0017] The present disclosure provides a pharmaceutical composition comprising a compound as described herein and a therapeutically active agent, wherein the
15 bioavailability of the therapeutically active agent is improved.

BRIEF DESCRIPTION OF THE FIGURES

[0018] **Figure 1** represents β -cyclodextrin (CD), Hydroxy propyl- β -cyclodextrin (HP- β -CD) and Sulfobutyl ether beta-cyclodextrin (SBE- β -CD).

[0019] **Figure 2** represents different types of polymers, namely poly(vinyl alcohol) [left] and polyketal [center] and polyethylene glycol [right].

[0020] **Figure 3** represents different types of endcapping group(s)/hydrophobic moieties, namely adamantane carboxylate [left], nor-adamantane carboxylate [center] and cholesterol carbamate [right].

[0021] **Figure 4** represents different types of linker group(s), namely ester, amide, carbonate carbamate and carbonyl.

[0022] **Figure 5** represents the general structure of covalent conjugates of Cyclodextrin Pendant Polymers.

[0023] **Figure 6** represents the general structure of non-covalent conjugates of Cyclodextrin Pendant Polymers.

[0024] **Figure 7** represents different types of polymers covalently conjugated with cyclodextrin, namely (PEG-Glycine-(Lysine- β -CD)₉) [left] and Poly(vinyl alcohol)-(β -CD)₇₅ [right].

[0025] **Figure 8** represents pADK polymer and graphical image represents the microparticles of pADK polymer non-covalently conjugated with cyclodextrin.

[0026] **Figure 9** represents schematic synthesis of pADK monomers and polymers. **Figure 9a** represents schematic synthesis of 2,2-dipropoxyglyoxypropane, and **Figure 9b** represents schematic synthesis of pADK polymers.

[0027] **Figure 10** represents different types of pendent polymeric backbone (PPB) non-covalently conjugated with cyclodextrin: Poly(vinyl alcohol)-(Adamantane)₆₅ [left], cyclodextrin:PEG-Glycine-(Lysine-Adamantane)₉ [center] and

cyclodextrin:PEG-Glycine-(Lysine-Cholesterol)₉ [right] cyclodextrin:pADK polymer.

[0028] **Figure 11** represents schematic mechanism of cholesterol mobilization from NPC cells by cyclodextrin pendant polymers.

- 5 [0029] **Figure 12** represents pADK microparticle response to methyl- β -CD. (A) SEM image of rhodamine encapsulated pADK microparticles (500 μ m scale bar); (B) Rhodamine release kinetics of pADK microparticles in the presence of methyl- β -CD (blue) and in PBS (red).

10 **DETAILED DESCRIPTION OF THE DISCLOSURE**

[0030] While the following terms are believed to be well understood by one of ordinary skill in the art, the following definitions are set forth to facilitate explanation of the presently disclosed subject matter.

- 15 [0031] Throughout the present specification, the terms “about” and/or “approximately” may be used in conjunction with numerical values and/or ranges. The term “about” is understood to mean those values near to a recited value. For example, “about 40 [units]” may mean within $\pm 25\%$ of 40 (e.g., from 30 to 50), within $\pm 20\%$, $\pm 15\%$, $\pm 10\%$, $\pm 9\%$, $\pm 8\%$, $\pm 7\%$, $\pm 6\%$, $\pm 5\%$, $\pm 4\%$, $\pm 3\%$, $\pm 2\%$, $\pm 1\%$, less than $\pm 1\%$, or any other value or range of values therein or there below.
- 20 Furthermore, the phrases “less than about [a value]” or “greater than about [a value]” should be understood in view of the definition of the term “about” provided herein. The terms “about” and “approximately” may be used interchangeably.

- [0032] Throughout the present specification, numerical ranges are provided for 25 certain quantities. It is to be understood that these ranges comprise all sub-ranges therein. Thus, for example the range “from 50 to 80” includes all possible ranges therein (e.g., 51-79, 52-78, 53-77, 54-76, 55-75, 60-70, etc.). Furthermore, all values within a given range may be an endpoint for the range encompassed

thereby (e.g., the range 50-80 includes the ranges with endpoints such as 55-80, 50-75, etc.).

5 [0033] The term "a" or "an" refers to one or more of that entity; for example, "a kinase inhibitor" refers to one or more kinase inhibitors or at least one kinase inhibitor. As such, the terms "a" (or "an"), "one or more" and "at least one" are used interchangeably herein. In addition, reference to "an inhibitor" by the indefinite article "a" or "an" does not exclude the possibility that more than one of the inhibitors is present, unless the context clearly requires that there is one and only one of the inhibitors.

10 [0034] As used herein, the verb "comprise" as is used in this description and in the claims and its conjugations are used in its non-limiting sense to mean that items following the word are included, but items not specifically mentioned are not excluded. The present invention may suitably "comprise", "consist of", or "consist essentially of", the steps, elements, and/or reagents described in the
15 claims.

[0035] It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely", "only" and the like in connection with the recitation of claim elements, or the use of a "negative" limitation.

20 [0036] The term "treating" means one or more of relieving, alleviating, delaying, reducing, reversing, improving, or managing at least one symptom of a condition in a subject. The term "treating" may also mean one or more of arresting, delaying the onset (i.e., the period prior to clinical manifestation of the condition) or reducing the risk of developing or worsening a condition.

25 [0037] An "effective amount" means the amount of a formulation according to the invention that, when administered to a patient for treating a state, disorder or condition is sufficient to effect such treatment. The "effective amount" will vary depending on the active ingredient, the state, disorder, or condition to be treated

and its severity, and the age, weight, physical condition and responsiveness of the mammal to be treated.

[0038] The term "therapeutically effective" applied to dose or amount refers to that quantity of a compound or pharmaceutical formulation that is sufficient to result in a desired clinical benefit after administration to a patient in need thereof.

[0039] All weight percentages (i.e., "% by weight" and "wt. %" and w/w) referenced herein, unless otherwise indicated, are measured relative to the total weight of the pharmaceutical composition.

[0040] As used herein, "substantially" or "substantial" refers to the complete or nearly complete extent or degree of an action, characteristic, property, state, structure, item, or result. For example, an object that is "substantially" enclosed would mean that the object is either completely enclosed or nearly completely enclosed. The exact allowable degree of deviation from absolute completeness may in some cases depend on the specific context. However, generally speaking, the nearness of completion will be so as to have the same overall result as if absolute and total completion were obtained. The use of "substantially" is equally applicable when used in a negative connotation to refer to the complete or near complete lack of action, characteristic, property, state, structure, item, or result. For example, a composition that is "substantially free of" other active agents would either completely lack other active agents, or so nearly completely lack other active agents that the effect would be the same as if it completely lacked other active agents. In other words, a composition that is "substantially free of" an ingredient or element or another active agent may still contain such an item as long as there is no measurable effect thereof.

[0041] The terms below, as used herein, have the following meanings, unless indicated otherwise:

"Amino" refers to the $-NH_2$ radical.

"Cyano" refers to the CN radical.

“Halo” or “halogen” refers to bromo, chloro, fluoro or iodo radical.

“Hydroxy” or “hydroxyl” refers to the OH radical.

“Imino” refers to the =NH substituent.

“Nitro” refers to the NO₂ radical.

5 “Oxo” refers to the =O substituent.

“Thioxo” refers to the =S substituent.

[0042] “Alkyl” or “alkyl group” refers to a fully saturated, straight or branched hydrocarbon chain radical having from one to twelve carbon atoms, and which is attached to the rest of the molecule by a single bond. Alkyls comprising any number of carbon atoms from 1 to 12 are included. An alkyl comprising up to 12 carbon atoms is a C1-C12 alkyl, an alkyl comprising up to 10 carbon atoms is a C1-C10 alkyl, an alkyl comprising up to 6 carbon atoms is a C1-C6 alkyl and an alkyl comprising up to 5 carbon atoms is a C1-C5 alkyl. A C1-C5 alkyl includes C5 alkyls, C4 alkyls, C3 alkyls, C2 alkyls and C1 alkyl (i.e., methyl). A C1-C6 alkyl includes all moieties described above for C1-C5 alkyls but also includes C6 alkyls. A C1-C10 alkyl includes all moieties described above for C1-C5 alkyls and C1-C6 alkyls, but also includes C7, C8, C9 and C10 alkyls. Similarly, a C1-C12 alkyl includes all the foregoing moieties, but also includes C11 and C12 alkyls. Non-limiting examples of C1-C12 alkyl include methyl, ethyl, n-propyl, i-propyl, sec-propyl, n-butyl, i butyl, sec-butyl, t-butyl, n-pentyl, t-amyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, and n-dodecyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0043] “Alkylene” or “alkylene chain” refers to a fully saturated, straight or branched divalent hydrocarbon chain radical, and having from one to twelve carbon atoms. Non-limiting examples of C1-C12 alkylene include methylene, ethylene, propylene, n butylene, ethenylene, propenylene, n butenylene, propynylene, n butynylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule

and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkylene chain can be optionally substituted.

[0044] “Alkenyl” or “alkenyl group” refers to a straight or branched hydrocarbon chain radical having from two to twelve carbon atoms, and having one or more carbon-carbon double bonds. Each alkenyl group is attached to the rest of the molecule by a single bond. Alkenyl group comprising any number of carbon atoms from 2 to 12 are included. An alkenyl group comprising up to 12 carbon atoms is a C2-C12 alkenyl, an alkenyl comprising up to 10 carbon atoms is a C2-C10 alkenyl, an alkenyl group comprising up to 6 carbon atoms is a C2-C6 alkenyl and an alkenyl comprising up to 5 carbon atoms is a C2-C5 alkenyl. A C2-C5 alkenyl includes C5 alkenyls, C4 alkenyls, C3 alkenyls, and C2 alkenyls. A C2-C6 alkenyl includes all moieties described above for C2-C5 alkenyls but also includes C6 alkenyls. A C2-C10 alkenyl includes all moieties described above for C2-C5 alkenyls and C2-C6 alkenyls, but also includes C7, C8, C9 and C10 alkenyls. Similarly, a C2-C12 alkenyl includes all the foregoing moieties, but also includes C11 and C12 alkenyls. Non-limiting examples of C2-C12 alkenyl include ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 4-octenyl, 5-octenyl, 6-octenyl, 7-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 4-nonenyl, 5-nonenyl, 6-nonenyl, 7-nonenyl, 8-nonenyl, 1-decenyl, 2-decenyl, 3-decenyl, 4-decenyl, 5-decenyl, 6-decenyl, 7-decenyl, 8-decenyl, 9-decenyl, 1-undecenyl, 2-undecenyl, 3-undecenyl, 4-undecenyl, 5-undecenyl, 6-undecenyl, 7-undecenyl, 8-undecenyl, 9-undecenyl, 10-undecenyl, 1-dodecenyl, 2-dodecenyl, 3-dodecenyl, 4-dodecenyl, 5-dodecenyl, 6-dodecenyl, 7-dodecenyl, 8-dodecenyl, 9-dodecenyl, 10-dodecenyl, and 11-dodecenyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0045] “Alkenylene” or “alkenylene chain” refers to a straight or branched divalent hydrocarbon chain radical, having from two to twelve carbon atoms, and having one or more carbon-carbon double bonds. Non-limiting examples of C2-C12 alkenylene include ethene, propene, butene, and the like. The alkenylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkenylene chain can be optionally substituted.

[0046] “Alkynyl” or “alkynyl group” refers to a straight or branched hydrocarbon chain radical having from two to twelve carbon atoms, and having one or more carbon-carbon triple bonds. Each alkynyl group is attached to the rest of the molecule by a single bond. Alkynyl group comprising any number of carbon atoms from 2 to 12 are included. An alkynyl group comprising up to 12 carbon atoms is a C2-C12 alkynyl, an alkynyl comprising up to 10 carbon atoms is a C2-C10 alkynyl, an alkynyl group comprising up to 6 carbon atoms is a C2-C6 alkynyl and an alkynyl comprising up to 5 carbon atoms is a C2-C5 alkynyl. A C2-C5 alkynyl includes C5 alkynyls, C4 alkynyls, C3 alkynyls, and C2 alkynyls. A C2-C6 alkynyl includes all moieties described above for C2-C5 alkynyls but also includes C6 alkynyls. A C2-C10 alkynyl includes all moieties described above for C2-C5 alkynyls and C2-C6 alkynyls, but also includes C7, C8, C9 and C10 alkynyls. Similarly, a C2-C12 alkynyl includes all the foregoing moieties, but also includes C11 and C12 alkynyls. Non-limiting examples of C2-C12 alkenyl include ethynyl, propynyl, butynyl, pentynyl and the like. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0047] “Alkynylene” or “alkynylene chain” refers to a straight or branched divalent hydrocarbon chain radical, having from two to twelve carbon atoms, and having one or more carbon-carbon triple bonds. Non-limiting examples of C2-C12 alkynylene include ethynylene, propargylene and the like. The alkynylene chain is attached to the rest of the molecule through a single bond and to the

radical group through a single bond. The points of attachment of the alkynylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkynylene chain can be optionally substituted.

- 5 [0048] “Alkoxy” refers to a radical of the formula ORa where Ra is an alkyl, alkenyl or alkynyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkoxy group can be optionally substituted.

- 10 [0049] “Alkylamino” refers to a radical of the formula -NHRa or -NRaRa where each Ra is, independently, an alkyl, alkenyl or alkynyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkylamino group can be optionally substituted.

- 15 [0050] “Alkylcarbonyl” refers to the $-C(=O)Ra$ moiety, wherein Ra is an alkyl, alkenyl or alkynyl radical as defined above. A non-limiting example of an alkyl carbonyl is the methyl carbonyl (“acetal”) moiety. Alkylcarbonyl groups can also be referred to as “Cw-Cz acyl” where w and z depicts the range of the number of carbon in Ra, as defined above. For example, “C1-C10 acyl” refers to alkylcarbonyl group as defined above, where Ra is C1-C10 alkyl, C1-C10 alkenyl, or C1-C10 alkynyl radical as defined above. Unless stated otherwise specifically
20 in the specification, an alkyl carbonyl group can be optionally substituted.

- [0051] “Aryl” refers to a hydrocarbon ring system radical comprising hydrogen, 6 to 18 carbon atoms and at least one aromatic ring. For purposes of this invention, the aryl radical can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems. Aryl radicals include, but are not
25 limited to, aryl radicals derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise

specifically in the specification, the term “aryl” is meant to include aryl radicals that are optionally substituted.

[0052] “Aralkyl” or “arylalkyl” refers to a radical of the formula $-R_b-R_c$ where R_b is an alkylene group as defined above and R_c is one or more aryl radicals as defined above, for example, benzyl, diphenylmethyl and the like. Unless stated otherwise specifically in the specification, an aralkyl group can be optionally substituted.

[0053] “Aralkenyl” or “arylalkenyl” refers to a radical of the formula $-R_b-R_c$ where R_b is an alkenylene group as defined above and R_c is one or more aryl radicals as defined above. Unless stated otherwise specifically in the specification, an aralkenyl group can be optionally substituted.

[0054] “Aralkynyl” or “arylalkynyl” refers to a radical of the formula $-R_b-R_c$ where R_b is an alkynylene group as defined above and R_c is one or more aryl radicals as defined above. Unless stated otherwise specifically in the specification, an aralkynyl group can be optionally substituted.

[0055] “Carbocyclyl,” “carbocyclic ring” or “carbocycle” refers to a rings structure, wherein the atoms which form the ring are each carbon. Carbocyclic rings can comprise from 3 to 20 carbon atoms in the ring. Carbocyclic rings include aryls and cycloalkyl, cycloalkenyl and cycloalkynyl as defined herein. Unless stated otherwise specifically in the specification, a carbocyclyl group can be optionally substituted.

[0056] “Cycloalkyl” refers to a stable non aromatic monocyclic or polycyclic fully saturated hydrocarbon radical consisting solely of carbon and hydrogen atoms, which can include fused or bridged ring systems, having from three to twenty carbon atoms, preferably having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkyl radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyl radicals include,

for example, adamantyl, norbornyl, decalanyl, 7,7 dimethyl bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkyl group can be optionally substituted.

[0057] "Heterocyclyl," "heterocyclic ring" or "heterocycle" refers to a stable 3 to 20 membered non aromatic ring radical which consists of two to twelve carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Heterocyclyl or heterocyclic rings include heteroaryls as defined below. Unless stated otherwise specifically in the specification, the heterocyclyl radical can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical can be optionally oxidized; the nitrogen atom can be optionally quaternized; and the heterocyclyl radical can be partially or fully saturated. Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolanyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholanyl, octahydroindolyl, octahydroisoindolyl, 2 oxopiperazinyl, 2 oxopiperidinyl, 2 oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4 piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholanyl, thiamorpholanyl, 1 oxo thiomorpholanyl, and 1,1 dioxo thiomorpholanyl. Unless stated otherwise specifically in the specification, a heterocyclyl group can be optionally substituted.

[0058] "N-heterocyclyl" refers to a heterocyclyl radical as defined above containing at least one nitrogen and where the point of attachment of the heterocyclyl radical to the rest of the molecule is through a nitrogen atom in the heterocyclyl radical. Unless stated otherwise specifically in the specification, a N-heterocyclyl group can be optionally substituted.

[0059] "Heteroaryl" refers to a 5 to 20 membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected

from the group consisting of nitrogen, oxygen and sulfur, and at least one aromatic ring. For purposes of this invention, the heteroaryl radical can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical can be optionally oxidized; the nitrogen atom can be optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4 benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indoliziny, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazoliny, quinoxaliny, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in the specification, a heteroaryl group can be optionally substituted.

[0060] "N-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. Unless stated otherwise specifically in the specification, an N-heteroaryl group can be optionally substituted.

[0061] "Heteroarylalkyl" refers to a radical of the formula R_b-R_f where R_b is an alkylene chain as defined above and R_f is a heteroaryl radical as defined above.

Unless stated otherwise specifically in the specification, a heteroarylalkyl group can be optionally substituted.

[0062] “Thioalkyl” refers to a radical of the formula -SR_a where R_a is an alkyl, alkenyl, or alkynyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, a thioalkyl group can be optionally substituted.

[0063] The term “substituted” used herein means any of the above groups (*i.e.*, alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, alkoxy, alkylamino, alkylcarbonyl, thioalkyl, aryl, aralkyl, carbocyclyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl) wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atoms such as, but not limited to: a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, and ester groups; a sulfur atom in groups such as thiol groups, thioalkyl groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, *N*-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkylarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups.

[0064] “Substituted” also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, “substituted” includes any of the above groups in which one or more hydrogen atoms are replaced with -NR_gR_h, -NR_gC(=O)R_h, -NR_gC(=O)NR_gR_h, -NR_gC(=O)OR_h, -NR_gSO₂R_h, -OC(=O)NR_gR_h, -OR_g, -SR_g, -SOR_g, -SO₂R_g, -OSO₂R_g, -SO₂OR_g, =NSO₂R_g, and -SO₂NR_gR_h. “Substituted also means any of the above groups in which one or

more hydrogen atoms are replaced with $-C(=O)R_g$, $-C(=O)OR_g$, $-C(=O)NR_gR_h$, $-CH_2SO_2R_g$, $-CH_2SO_2NR_gR_h$. In the foregoing, R_g and R_h are the same or different and independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl. “Substituted” further means any of the above groups in which one or more hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl group. In addition, each of the foregoing substituents can also be optionally substituted with one or more of the above substituents.

[0065] As used herein, the symbol “ $\frac{\text{---}}{\text{---}}$ ” (hereinafter can be referred to as “a point of attachment bond”) denotes a bond that is a point of attachment between two chemical entities, one of which is depicted as being attached to the point of attachment bond and the other of which is not depicted as being attached to the point of attachment bond. For example, “ $XY\frac{\text{---}}{\text{---}}$ ” indicates that the chemical entity “XY” is bonded to another chemical entity via the point of attachment bond. Furthermore, the specific point of attachment to the non depicted chemical entity can be specified by inference. For example, the compound CH_3R^3 , wherein R^3 is H or “ $XY\frac{\text{---}}{\text{---}}$ ” infers that when R^3 is “XY”, the point of attachment bond is the same bond as the bond by which R^3 is depicted as being bonded to CH_3 .

[0066] The following description includes information that may be useful in understanding the present invention. It is not an admission that any of the

information provided herein is prior art or relevant to the presently claimed inventions, or that any publication specifically or implicitly referenced is prior art.

[0067] The present disclosure is addressed to the aforementioned needs of the art and provides guest:host complexes and their application as a therapeutic agent containing drug delivery system useful for removing cholesterol from the cells.

[0068] In a non-limiting embodiment of the present disclosure, the guest includes but is not limited to a polymer.

[0069] In another non-limiting embodiment of the present disclosure, the host includes but is not limited to macrocyclic compounds, wherein said macrocyclic compound is cyclodextrin or its derivatives.

[0070] The present disclosure relates to pendant polymer:cyclodextrin conjugates.

[0071] In an embodiment of the present disclosure, the polymer of the aforesaid pendant polymer:cyclodextrin conjugate comprises a polymer backbone that is modified with β -cyclodextrin or its derivative.

[0072] In another non-limiting embodiment of the present disclosure, the polymer:cyclodextrin conjugate is a covalent conjugate or a non-covalent conjugate. In particular, the polymer:cyclodextrin conjugate includes but is not limited to “covalent conjugates of polymers with cyclodextrin” and “non-covalent conjugates of polymers with cyclodextrin” and their combination.

[0073] In an embodiment related to covalent conjugates of polymers with cyclodextrin, the polymer is attached to the cyclodextrin through a linker. Thus, in an exemplary embodiment, the covalent polymer:cyclodextrin conjugate is represented as polymer-linker-cyclodextrin.

[0074] In an embodiment related to non-covalent conjugates of polymers with cyclodextrin, hydrophobic moiety of a Pendant Polymeric Backbone (PPB) is complexed with cyclodextrin, wherein the PPB is composed of polymer attached

with hydrophobic moiety through linker i.e. polymer-linker-hydrophobic moiety. Thus, in an exemplary embodiment, the non-covalent polymer:cyclodextrin conjugate is represented as polymer-linker-hydrophobic moiety-cyclodextrin.

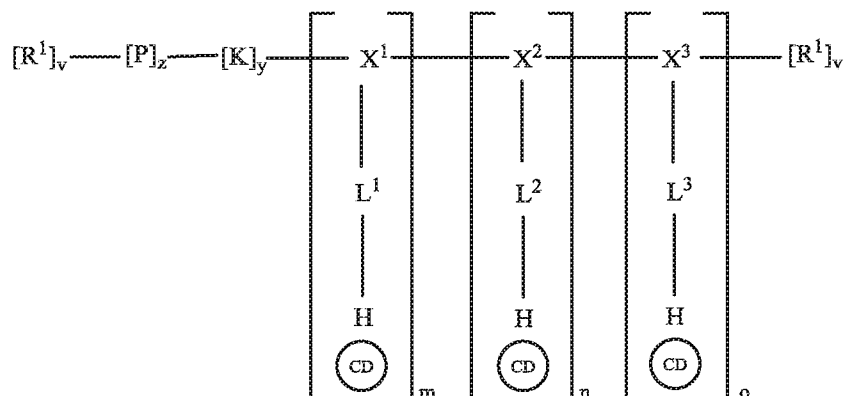
5 [0075] As used herein, the expressions “polymer:cyclodextrin conjugate”, “polymer:cyclodextrin complex”, “polymer:cyclodextrin molecule”, “conjugate of polymer with cyclodextrin”, “conjugate” and “polymer:cyclodextrin nanoparticle” are employed interchangeably within the instant disclosure and refer to the polymer:cyclodextrin compound/therapeutic molecule/product of the instant disclosure.

10

[0076] As used herein, the expressions “covalent polymer”, “covalent conjugate”, “covalent complex”, “covalent conjugate of polymer with cyclodextrin” and “Covalent Cyclodextrin Polymer” are employed interchangeably within the instant disclosure and refer to complex containing polymer covalently linked with
15 cyclodextrin.

[0077] As used herein, the expressions “non-covalent polymer”, “non-covalent conjugate”, “non-covalent complex”, “non-covalent conjugate of polymer with cyclodextrin” and “non-covalent Cyclodextrin Polymer” are employed
20 interchangeably within the instant disclosure and refer to complex containing polymer non-covalently linked with cyclodextrin.

[0078] The present disclosure provides a compound comprising the following structure:



wherein

5 R^1 is independently 2-hydroxy propyl, 1-hydroxy methyl, OH, CO_2H or NH_2 ;

P is a polymer;

X^1 , X^2 and X^3 are each backbone moieties;

10 L^1 , L^2 , L^3 and K are each linker moieties, wherein each of L^1 , L^2 and L^3 may be present or absent, provided at least one of L^1 , L^2 and L^3 is present;

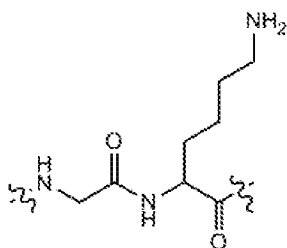
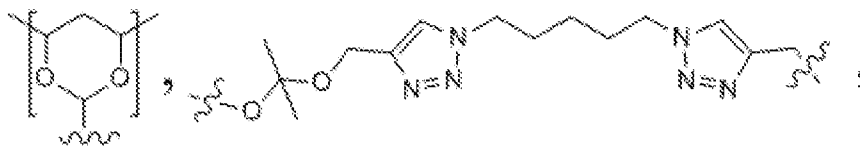
H is host moiety attached directly to the backbone moiety or via the linker moiety;

CD is a cyclodextrin, or a derivative thereof; wherein CD is non-covalently conjugated to H;

15 m, n and o are each independently from 0 to 1000, wherein at least one of m, n and o is at least 4; and

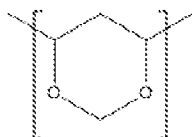
v, z and y are each independently 0 to 500.

[0079] In a non-limiting embodiment of the present disclosure, each instance of X^1 , X^2 and X^3 is independently selected from C_1 - C_4 hydroxyalkyl, $(C_1$ - C_4 alkyl)-O- $(C_1$ - C_4 alkyl)-O- $(C_1$ - C_4 alkyl), $(C_1$ - C_4 alkyl)-O- $(C_1$ - C_4 alkyl), peptide, Gly-Lys,



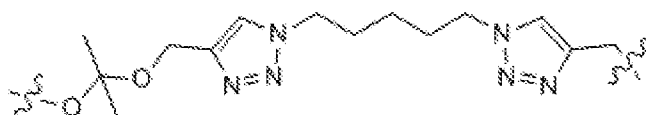
10 or an amino acid;

wherein when X^1 or X^2 or X^3 is independently



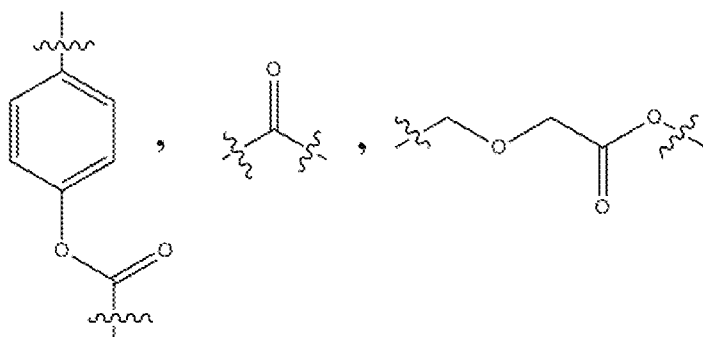
15 the linker moiety or hydrophobic moiety is directly attached to C1 carbon of cyclic ketal moiety; and

wherein when X^1 or X^2 or X^3 is independently



the linker moiety or hydrophobic moiety is directly attached to C3 carbon of pentane chain.

[0080] In a non-limiting embodiment of the present disclosure, L^1 , L^2 , L^3 and K independently is selected from an alkyl ester, an alkyl amide, an alkyl carbonate, an alkyl carbamate,



or Ar^1 , wherein Ar^1 is an optionally substituted 5- or 6- membered aryl, heteroaryl comprising 1, 2, 3 or 4 heteroatoms individually selected from N, O, and S.

[0081] In a non-limiting embodiment of the present disclosure, Ar^1 is triazole.

[0082] In a non-limiting embodiment of the present disclosure, the polymer is selected from poly vinyl alcohol, polyketal or polyethylene glycol.

[0083] In a non-limiting embodiment of the present disclosure, the cyclodextrin or its derivative employed in the conjugate includes but is not limited to β -cyclodextrin (Figure 1), α -cyclodextrin, γ -cyclodextrin, derivatives thereof, or combinations thereof.

[0084] In a non-limiting embodiment of the present disclosure, the cyclodextrin derivative is selected from a group comprising Hydroxy propyl β -cyclodextrin (HP- β -CD), Sulfobutyl ether- β -cyclodextrin (SBE- β -CD), Methyl- β -cyclodextrin (Me- β -CD, and other charged or uncharged derivatives of β -CD derivatives thereof, or combinations thereof.

[0085] In a non-limiting embodiment of the present disclosure, the alkyl group in hydroxyalkyl- α -cyclodextrin, hydroxyalkyl- β -cyclodextrin, hydroxyalkyl- γ -cyclodextrin or their derivatives is selected from C₁-C₁₀ linear alkyl, C₁-C₁₀ branched alkyl or C₁-C₁₀ cycloalkyl, each having one or more optional
5 substituents.

[0086] In a non-limiting embodiment of the present disclosure, the H is selected from cycloalkyl, heterocycloalkyl, aryl or heterocycloaryl.

[0087] In another non-limiting embodiment of the present disclosure, the H is adamantane, noradamantane or cholesterol.

10 [0088] In a non-limiting embodiment of the present disclosure, m, n and o are each independently from 0 to 1000.

[0089] In another non-limiting embodiment of the present disclosure, m, n and o are each independently from 0 to 100.

15 [0090] In a preferred embodiment, m, n and o are each independently from 3 to 30.

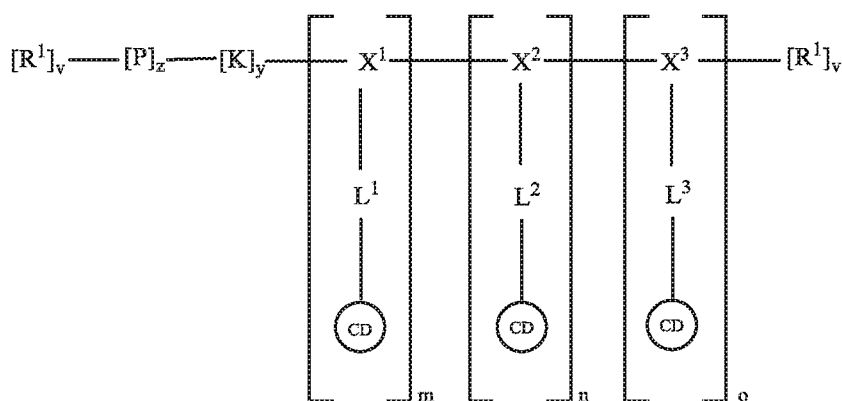
[0091] In another preferred embodiment, m, n and o are each independently from 10 to 100.

[0092] In yet another preferred embodiment, m, n and o are each independently from 15 to 65.

20 [0093] In still another preferred embodiment, m, n and o are each independently from 20 to 30.

[0094] In still another preferred embodiment, m, n and o are each independently from 50 to 65.

[0095] The present disclosure provides a compound comprising the following structure:



wherein

5 R^1 is independently 2-hydroxy propyl, 1-hydroxy methyl, OH, CO_2H or NH_2 ;

P is a polymer;

X^1 , X^2 and X^3 are each backbone moieties;

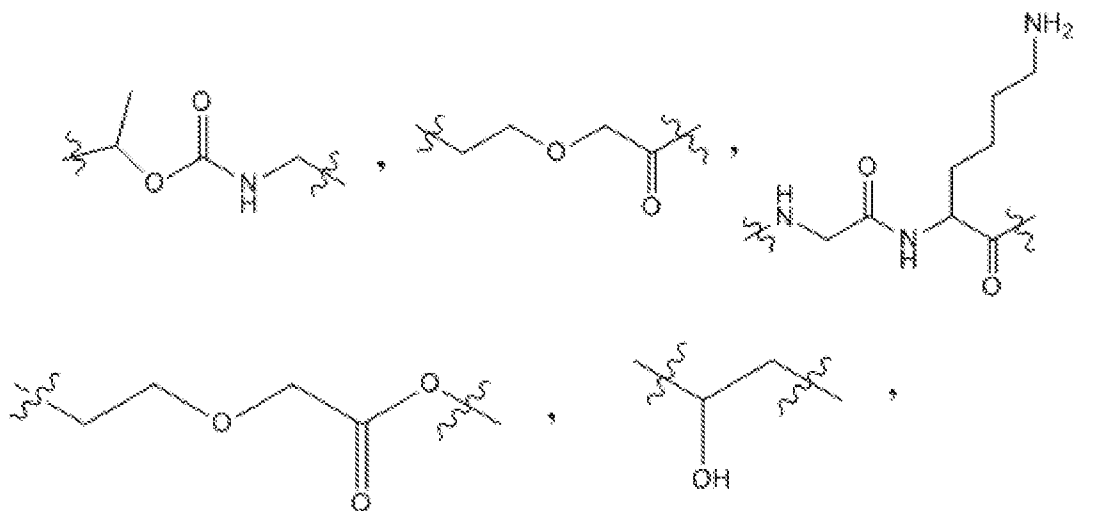
10 L^1 , L^2 , L^3 and K are each linker moieties, wherein each of L^1 , L^2 and L^3 may be present or absent, provided at least one of L^1 , L^2 and L^3 is present;

CD is a cyclodextrin, or a derivative thereof, wherein each CD is covalently attached to respective L^1 , L^2 , L^3 ; and

m, n and o are each independently from 0 to 1000, wherein at least one of m, n and o is at least 4; and

15 v, z and y are each independently 0 to 500.

[0096] In a non-limiting embodiment of the present disclosure, each instance of X^1 , X^2 and X^3 is independently selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 hydroxyalkyl, $(C_1$ - C_4 alkyl)-O-(C_1 - C_4 alkyl)-O-(C_1 - C_4 alkyl), $(C_1$ - C_4 alkyl)-O-(C_1 - C_4 alkyl), alkyl ester, peptide, Gly-Lys,



or an amino acid; wherein when X^1 or X^2 or X^3 is independently Gly-Lys, the linker moiety is attached to omega amino group of Lysine.

[0097] In a non-limiting embodiment of the present disclosure, the polymer includes but is not limited to polyketal, poly(vinyl alcohol), polyethylene glycol, polysaccharide, polyester, polycarbonate, or polyamide, and combinations thereof.

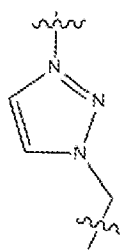
[0098] In a preferred embodiment of the present disclosure, the polymer is selected from a group comprising polyketal, poly(vinyl alcohol) and polyethylene glycol (Figure 2).

[0099] In a non-limiting embodiment of the present disclosure, the cyclodextrin or a derivative thereof is selected from α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin, hydroxyalkyl- α -cyclodextrin, hydroxyalkyl- β -cyclodextrin, hydroxyalkyl- γ -cyclodextrin, derivatives thereof, or combinations thereof.

[00100] In a non-limiting embodiment of the present disclosure, the alkyl in hydroxyalkyl- α -cyclodextrin, hydroxyalkyl- β -cyclodextrin, hydroxyalkyl- γ -cyclodextrin or their derivatives selected from C_1 - C_{10} linear alkyl, C_1 - C_{10} branched alkyl or C_1 - C_{10} cycloalkyl, each having one or more optional substituents.

[00101] In a non-limiting embodiment of the present disclosure, each of L¹, L² and L³ independently is selected from an alkyl, an alkyl ester, an alkyl amide, an alkyl carbonate, an alkyl carbamate, or Ar¹, wherein Ar¹ is an optionally substituted 5- or 6- membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms
5 individually selected from N, O, and S.

[00102] In another embodiment of the present disclosure, Ar¹ is an optionally substituted triazole or



[00103] In a non-limiting embodiment of the present disclosure, m, n and o
10 are each independently from 0 to 1000.

[00104] In another non-limiting embodiment of the present disclosure, m, n and o are each independently from 0 to 100.

[00105] In a preferred embodiment, m, n and o are each independently from 3 to 30.

15 [00106] In another preferred embodiment, m, n and o are each independently from 10 to 100.

[00107] In yet another preferred embodiment, m, n and o are each independently from 15 to 65.

[00108] In still another preferred embodiment, m, n and o are each
20 independently from 20 to 30.

[00109] In still another preferred embodiment, m, n and o are each independently from 50 to 65.

[00110] The polymers of the present invention can be long circulating, biocompatible, and can substantially increase cholesterol clearance from cells, specifically NPC deficient cells. Further, the said polymers can deliver multiple “copies/units” of cyclodextrin or its derivatives e.g., β -CD/HP- β -CD/SBE- β -CD
5 to the lysosomes of cells.

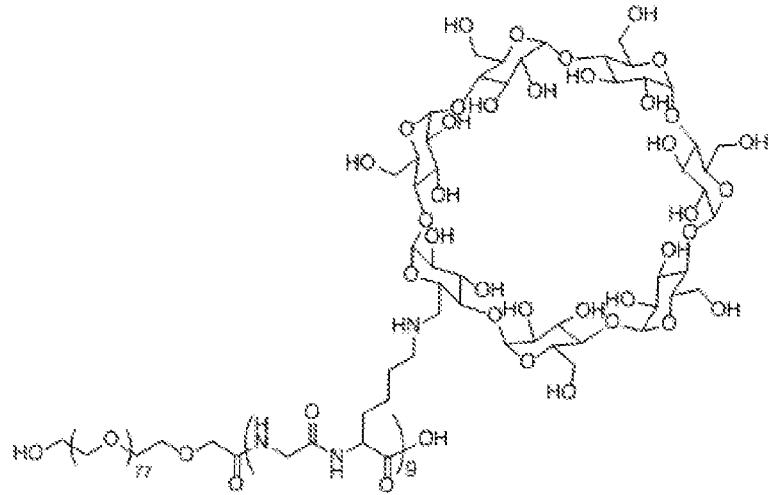
[00111] In yet another non-limiting embodiment of the present disclosure, the linker employed in the conjugate includes but is not limited to bio-degradable linker.

[00112] In another non-limiting embodiment of the present disclosure, the
10 linker is selected from a group comprising acetal, amide, ketal, orthoester, ester, vinyl ether, carbamate, carbonyl, hydrazine, triazole, phenoxy, and combinations thereof.

[00113] In a non-limiting embodiment of the present disclosure, the hydrophobic moiety employed in the conjugate includes but is not limited to
15 cholesterol, adamantane, noradamantane, cyclohexane, dodecane, its derivatives and combinations thereof.

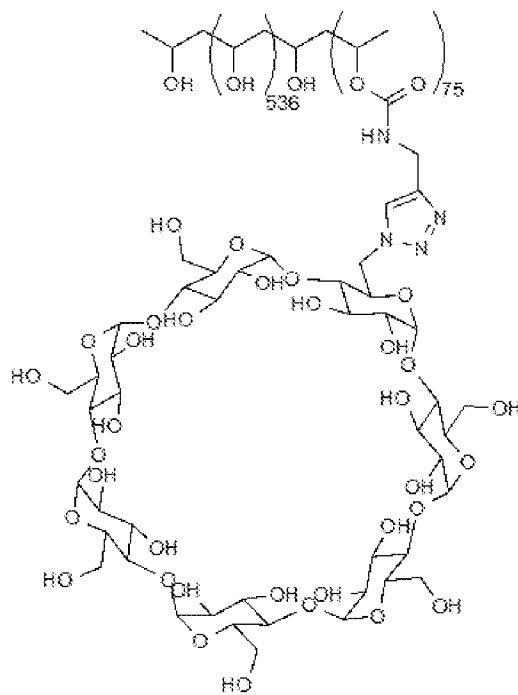
[00114] In exemplary embodiments, the covalent polymer:cyclodextrin conjugate of the present disclosure is provided in Figure 7, PEG-[Glycine-(Lysine- β -CD)]₉ and Poly(vinyl alcohol)-trz-(β -CD)₇₅ and the non-covalent
20 polymer:cyclodextrin conjugate of the present disclosure is provided in Figures 8, (conjugate of Polyadamantane-trz-ketal and β -cyclodextrin). Pendent polymeric backbone (PPB) viz. polymer-linker-hydrophobic moiety of non-covalent polymer:cyclodextrin conjugates of the present disclosure is provided in Figures 8 and 10, Polyadamantane-trz-ketal, Poly(vinyl alcohol)-(Adamantane)₆₅, PEG-
25 [Glycine-(Lysine-Adamantane)]₉ and PEG-[Glycine-(Lysine-Cholesterol)]₉.

[00115] The present disclosure provides a compound selected from:

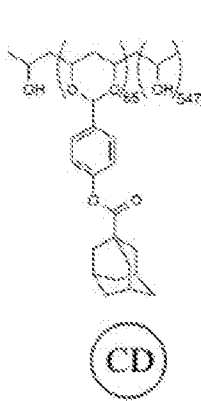


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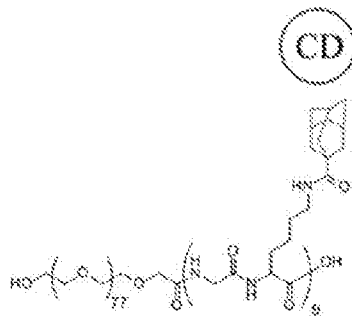
PEG-[Glycine-(Lysine-β-CD)]₉



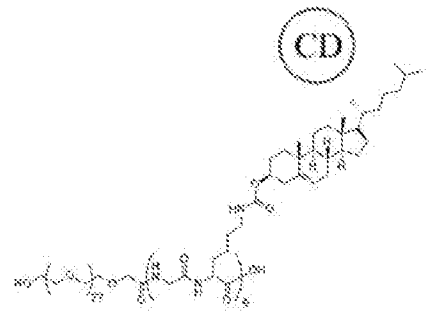
Poly(vinyl alcohol)-triaz-(β-CD)₇₅



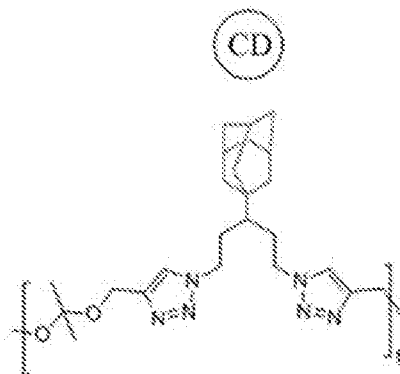
**Poly(vinyl alcohol)-
(Adamantane)₆₅
complexed with CD**



**PEG-[Glycine-(Lysine-
Adamantane)]₉
complexed with CD**



**PEG-[Glycine-(Lysine-
Cholesterol)]₉
complexed with CD**



wherein 't' ranges from 5 to 500

**pADK polymer
complexed with CD**

[00116] The present disclosure thus provide non-covalent polymer:cyclodextrin conjugates. In an embodiment, said non-covalent conjugate comprises polymer, linker, hydrophobic moiety and cyclodextrin.

[00117] In a specific embodiment, the non-covalent conjugate is represented as polymer-linker-hydrophobic moiety-cyclodextrin (Figure 6). The polymer, linker, hydrophobic moiety and cyclodextrin groups of the non-covalent

polymer:cyclodextrin conjugates are selected from the groups/alternatives provided in the above embodiments.

[00118] In a preferred embodiment, the non-covalent polymer:cyclodextrin conjugate of the present disclosure comprises polyketal as the polymer along with
5 linker, adamantane as the hydrophobic moiety and cyclodextrin. Thus, the present disclosure provides polyketal polymer based non-covalent conjugates of polymer:cyclodextrin. In a specific embodiment, the polyketal polymer based non-covalent conjugate comprises polyketal, triazole based linker, adamantane and cyclodextrin. In an exemplary embodiment, a polyketal polymer based non-
10 covalent conjugate is provided in Figure 8. In other embodiments, the non-covalent conjugate comprises 'ketal or polyketal' in combination with any linker, hydrophobic moiety and cyclodextrin/cyclodextrin derivative.

[00119] The present disclosure further provide covalent polymer:cyclodextrin conjugates. In an embodiment, said covalent conjugate
15 comprises polymer, linker and cyclodextrin. In a specific embodiment, the covalent conjugate is represented as polymer-linker-cyclodextrin Figure 5. The polymer, linker and cyclodextrin groups of the covalent polymer:cyclodextrin conjugates are selected from the groups/alternatives provided in the previous embodiments.

20 [00120] In a preferred embodiment, the covalent polymer:cyclodextrin conjugate of the present disclosure comprises polyketal as the polymer along with linker and cyclodextrin attached to the backbone. Thus, the present disclosure provides polyketal polymer based covalent conjugates of polymer:cyclodextrin. In a specific embodiment, the polyketal polymer based covalent conjugate comprises
25 polyketal, triazole based linker and cyclodextrin. In other embodiments, covalent conjugate comprise 'polyketal' in combination with any linker and cyclodextrin/cyclodextrin derivative.

[00121] In an embodiment of the present disclosure, the polymer:cyclodextrin conjugate including covalent conjugate and non-covalent conjugate, is a nanoparticle or nanocarrier system.

[00122] The present disclosure also relates to a process for preparing guest:host complex. In a non-limiting embodiment, the guest includes but is not limited to polymer. In another non-limiting embodiment, the host includes but is not limited to macrocyclic compounds, wherein said macrocyclic compound is cyclodextrin or its derivatives.

[00123] Thus, a non-limiting embodiment of the present disclosure relates to the synthesis of pendant polymer:cyclodextrin complexes.

[00124] In a preferred embodiment of the present disclosure, the aforementioned process includes but is not limited to the process for preparing “covalent conjugates of polymers with cyclodextrin” and “non-covalent conjugates of polymers with cyclodextrin” and their combination.

[00125] In the process for preparing covalent conjugates of polymers with cyclodextrin, the cyclodextrin is attached directly to polymeric backbone via a linker to afford the final complex. In a specific embodiment of the present disclosure, the process of preparing covalent conjugate comprises steps of:

1. Synthesis of a polymeric backbone such as polypeptide, polydisulfide, polyketal, or poly(vinyl) through synthetic techniques selected from solid phase peptide synthesis or polymerization techniques, or a combination thereof, wherein the synthesized polymer is usually designed to have a reactive modifiable linker side-chain such as an amine, hydroxy, alkyne, or azide; and

2. Covalent attachment of cyclodextrin to the polymeric backbone via the linker side-chain through variety of chemistries.

[00126] In an embodiment, for linker side chains such as amine or hydroxy, mono-tosylated β -CD can be used as a reactive intermediate for the displacement of the tosyl group by the reactive amine or hydroxy group. In another

embodiment, for linker sidechains such as alkyne or azide, the inverse reactive group, that is, mono-azido β -CD or mono-alkynyl β -CD can be used to attach to the polymer via a 1,3-dipolar cycloaddition reaction.

[00127] In an exemplary embodiment, representative molecules of covalent
5 conjugates of polymers with cyclodextrin are PEG-[Glycine-(Lysine- β -CD)]₉ and Poly(vinyl alcohol)-trz-(β -CD)₇₅ as shown in Figure 7.

[00128] In the process for preparing non-covalent conjugates, cyclodextrin is complexed with hydrophobic moiety of the Pendant Polymeric Backbone (PPB) to obtain non-covalent conjugates of polymers with cyclodextrin. In an
10 embodiment, the process of preparing non-covalent conjugate comprises steps of:

1. Dissolving the pendant polymer with hydrophobic guest group in an appropriate solvent based on the application such as DMSO, water, or buffer, or any combination thereof.

2. Separately dissolving the cyclodextrin or cyclodextrin derivatives in
15 water or buffer or a combination thereof based on the application.

3. Mixing the pendant polymer and cyclodextrin solutions in a 1:1 molar ratio of the hydrophobic group to cyclodextrin to afford the final complexed solutions.

[00129] In an exemplary embodiment, representatives of Pendant
20 Polymeric Backbone (PPB) are polyketal-trz-adamantane (pADK) as shown in Figure 8, Poly(vinyl alcohol)-(Adamantane)₆₅, PEG-[Glycine-(Lysine-Adamantane)]₉ and PEG-[Glycine-(Lysine-Cholesterol)]₉ as shown in Figure 10.

[00130] In the aforesaid process for preparing non-covalent conjugates of
the present disclosure, hydrophobic groups selected from a group comprising
25 Adamantane, Cholesterol and any other group known to form guest:host complexes with cyclodextrin is attached to the polymeric backbone (guest). The guest pendant polymer is then complexed with cyclodextrin or its derivative in a

ratio of one pendant group to one cyclodextrin or its derivative to afford the non-covalent conjugates.

[00131] In an exemplary embodiment, a non-covalent conjugate of polymer with cyclodextrin is pADK:β-CD is shown in Figure 8. pADK polymer repeating unit 't' value [number of repeating units] ranges from 5 to 500 and molecular weight ranges from 3000 to 300000.

[00132] In an aspect of the present disclosure, a process for preparing pendant polymers is also provided. The pendant polymers can be synthesized by first producing the polymeric backbone either by solid phase peptide synthesis, bacterial cell culture, or synthetic polymerization techniques with -OH, -SH, -NH₂, -N₃, alkyne or any other functional group side chains that can allow for easy conjugation of the guest molecule or cyclodextrin directly.

[00133] The present disclosure also relates to a method for managing or treating lipid storage disorders/lipidoses comprising administering a therapeutically effective amount of the host:guest conjugates such as, polymer:cyclodextrin conjugate. In an embodiment, said polymer:cyclodextrin conjugate is selected from a group comprising non-covalent conjugate, covalent conjugate, or a combination thereof. Said non-covalent and covalent conjugates are described in above paragraphs of the present specification.

[00134] In an embodiment of the present disclosure, the lipid storage disorder is lysosomal lipid storage disorder. In another embodiment, the lysosomal lipid storage disorder is selected from a group comprising sphingolipidoses, and wolman disease, or any combination thereof. In yet another embodiment, the sphingolipidoses are selected from a group comprising Niemann-Pick type C (NPC), Fabry disease, Krabbe disease, Gaucher disease, Tay-Sachs disease, Metachromatic leukodystrophy, multiple sulfatase deficiency and Farber disease, or any combination thereof. In an exemplary embodiment, the present method is for managing or treating Niemann-Pick type C (NPC).

[00135] The present disclosure provides a method for managing or treating lipid storage disorder/lipidose comprising administering a therapeutically effective amount of the host: guest conjugates such as, polymer:cyclodextrin conjugate, wherein said conjugate is a non-covalent conjugate or a covalent conjugate disclosure comprising polyketal as the polymer. In an embodiment of this method, said polyketal containing non-covalent conjugate comprises polyketal polymer, linker, hydrophobic moiety and cyclodextrin or its derivative. In a specific embodiment of this method, non-covalent conjugate comprises polyketal, triazole based linker, adamantane and cyclodextrin. In other 5 10 15 20 25
embodiments, the non-covalent conjugate comprises 'polyketal' in combination with any linker, hydrophobic moiety and cyclodextrin/cyclodextrin derivative. In an exemplary embodiment of the method, the lipid storage disorder is Niemann–Pick type C (NPC).

[00136] As used in the present disclosure, "management" or "managing" refers to preventing a disease or disorder or condition from occurring in a subject, decreasing the risk of death due to a disease or disorder or condition, delaying the onset of a disease or disorder or condition, inhibiting the progression of a disease or disorder or condition, partial or complete cure of a disease or disorder or condition and/or adverse effect attributable to the said disease or disorder or condition, obtaining a desired pharmacologic and/or physiologic effect (the effect may be prophylactic in terms of completely or partially preventing a disorder or disease or condition, or a symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease or disorder or condition and/or adverse effect attributable to the disease or disorder), relieving a disease or disorder or condition (i.e. causing regression of the disease or disorder or condition).

[00137] The present disclosure also provides a pharmaceutical composition or formulation comprising a therapeutically effective amount of polymer:cyclodextrin conjugate, optionally along with excipient(s).

[00138] In an embodiment of the present disclosure, the excipient is selected from a group comprising, but not limited to, granulating agent, binding agent, lubricating agent, disintegrating agent, sweetening agent, glidant, anti-adherent, anti-static agent, surfactant, anti-oxidant, gum, coating agent, coloring agent, flavouring agent, coating agent, plasticizer, preservative, suspending agent, emulsifying agent, plant cellulosic material, spheronization agents and combinations thereof.

[00139] In a non-limiting embodiment of the present disclosure, the pharmaceutical composition further comprises a therapeutically active agent.

10 [00140] In a non-limiting embodiment of the present disclosure, the pendent polymer:cyclodextrin conjugates are administered by mode selected from group comprising intravenous, subcutaneous, transdermal, intrathecal, oral and any other compatible mode, or any combination thereof.

[00141] In another embodiment of the present disclosure, the pharmaceutical composition/formulation is formulated into forms selected from a group comprising, but not limited to, solution, aqueous suspension, capsule, tablet, injection, cream, gel, ointment, lotion, emulsion, foam, troche, lozenge, oily suspension, patch, dentifrice, spray, drops, dispersible powder or granule, syrup, elixir, food stuff, and any combination of forms thereof.

20 [00142] In another embodiment, the present disclosure provides a method of treating a disease or a condition associated with abnormal NPC1 and/or NPC2 protein production, comprising administering to a subject in need thereof a compound or a composition as described herein.

[00143] In another embodiment, the present disclosure provides a method of treating lipid storage disorder comprising administering to a subject in need thereof a compound or a composition as described herein.

[00144] In another embodiment, the present disclosure provides a method of treating Niemann-Pick disease, comprising administering to a subject in need thereof a compound or a composition as described herein.

[00145] In another embodiment, the present disclosure provides a compound as described herein where the compound has an elimination half-life of
5 from about 6 hours to about 24 hours.

[00146] In another embodiment, the present disclosure provides a pharmaceutical composition comprising a compound as described herein and a therapeutically active agent, wherein the bioavailability of the therapeutically
10 active agent is improved.

[00147] Upon administration of the present pendent polymer:cyclodextrin conjugates, said conjugates accumulates in different organs in the body such as liver, kidney, lungs, spleen and brain. Once in the organs and upon cellular internalization, the polymers enter the cells and disassemble to afford free
15 cyclodextrins, allowing the cyclodextrins to complex with the excess cholesterol in the lysosomes and removing them from there. This removal of cholesterol then reduces the diseased state of the cells/organs hence affording the therapeutic effect. The Schematic mechanism of cholesterol mobilization from NPC cells by cyclodextrin pendant polymers of the present disclosure is shown in Figure 11.

[00148] The pendant polymer technology approach adopted in the present invention helps to increase the retention time of the drug in the body and hence shows prolonged therapeutic action because of the reduced rate of renal clearance due to its large size (>10 nm) and presence of polymeric moiety. Due to this, the dose required to maintain therapeutic concentrations are significantly reduced due
20 to the prolonged circulation time in the body. This in turn potentially results in less frequent administrations and intravenous administration which increases patient compliance drastically.

[00149] The present invention further discloses the use of polymer:cyclodextrin conjugate including covalent/non-covalent conjugate, or compositions/formulations comprising the same for management of lipid storage disorders, preferably lysosomal lipid storage disorders, and more preferably, 5 Niemann-pick disease type C.

[00150] Additional embodiments and features of the present disclosure will be apparent to one of ordinary skill in art based upon description provided herein. The embodiments herein and the various features and advantageous details thereof are explained with reference to the non-limiting embodiments in the description. 10 Descriptions of well-known/conventional methods and techniques are omitted so as to not unnecessarily obscure the embodiments herein. The examples presented herein are intended merely to facilitate an understanding of ways in which the embodiments herein may be practiced and to further enable those of skill in the art to practice the embodiments herein. Accordingly, the following examples should 15 not be construed as limiting the scope of the present disclosure.

EXAMPLES

COVALENT POLYMER CONJUGATES:

Example 1: Procedure for synthesis of PEG-Glycine-(Lysine- β -CD)₉

5 Step 1: Synthesis of CBz-G-(K)₉:

[00151] The polypeptide of sequence Glycine-(Lysine)₉ is synthesized using an Fmoc-based, solid-phase strategy on the Wang resin. The peptide is purified to homogeneity by reverse-phase HPLC and characterized by ¹H NMR, MS, and HPLC. The synthesized peptide is produced with a CBz-protected N-terminus glycine.
10

Step 2: Synthesis of CBz-G-(K- β -CD)₉:

[00152] 100mg (0.055mmol) of the polypeptide from the previous step is dissolved in 5ml dry DMSO under N₂. To this solution, 0.15mL (0.825 mmol, 1.6eq) of diisopropylethylamine is added and stirred, followed by addition of 2.8g (2.2mmol, 40eq) of β -CD-monotosylate. The reaction mixture is stirred overnight under N₂ atmosphere after which it is dialyzed exhaustively against DMSO (thrice), followed by deionized water (thrice) using a 2000 MWCO dialysis membrane to remove any unreacted β -CD and base. The dialyzed sample is then lyophilized to afford a dry powder. The product is then analyzed by ¹H NMR, HPLC, and GPC.
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Step 3: Synthesis of PEG-G-(K- β -CD)₉:

[00153] The CBz group is deprotected using conventional catalytic hydrogenation in presence of Pd/C followed by purification by dialysis to afford the deprotected Ad modified peptide. This is then reacted with heterobifunctional PEG modified with the NHS group at one terminus in presence of base to afford the final PEGylated peptide which is purified by dialysis as mentioned before. The final product is analyzed by ¹H NMR, HPLC, and GPC.
25

Preparing Composition of PEG-G-(K- β -CD)₉:

[00154] The number of CDs are variable based on the lysines in the polypeptide and can be varied from 6 to 15. The MW of the Poly(ethylene glycol) used here is 3400 (i.e. 77 EO units); however larger or smaller MW PEG can also
5 be used. In some instances, Glutathione or other targeting ligands could be attached to the other end of PEG to increase uptake of polymers in the brain.

Example 2: Procedure for synthesis of Poly(vinyl alcohol)-(β -CD)₇₅

Step 1: Synthesis of Alkyne-PVA:

10 [00155] Poly(vinyl alcohol) (MW = 27 kDa) (500 mg, 0.019 mmol) is added to 20 mL dry DMSO and purged with N₂. The suspension is then heated to 60°C, followed by addition of 308mg of N,N' carbonyldiimidazole (1.9mmol, 100eq). The reaction mixture is allowed to stir at room temperature for 24 hours followed by addition of 121 μ L Propargyl amine (1.9 mmol, 100 equivalents).
15 The reaction mixture is further allowed to stir for 24 hours followed by exhaustive dialysis against DMSO (thrice), and deionized water (thrice), in a dialysis membrane (12,000 – 14,000 Da MWCO). The dialyzed product is then lyophilized to afford the final product. The final product is analysed by ¹H NMR to determine the number alkyne groups attached.

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Step 2: Synthesis of Poly(vinyl alcohol)-trz-(β -CD)₇₅:

[00156] The alkyne-PVA was reacted with monoazido- β -CD (150 eq) in the presence of Sodium Ascorbate, Copper Sulfate, Diisopropylamine, in a mixture of 20 mL DMSO:Water (1:1). The reaction mixture is allowed to stir for
25 24 hours followed by purification by dialysis to remove any small molecule impurities. The dialyses is carried out against DMSO (thrice), dilute EDTA solution (thrice), deionized water (thrice), followed by lyophilization to afford the product as a white powder. The product is analysed by ¹H NMR, GPC to determine the number of CDs attached and the avg. MW.

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[00157] The number of CDs in the *PEG-G-(K-β-CD)*₉ can be as high as 200 – 300. In some instances, PEG can also be grafted on the PVA backbone to increase blood circulation time.

5 NON-COVALENT POLYMER CONJUGATES:

Example 3: Procedure for synthesis of Polyadamantane-ketal:cyclodextrin conjugates (Figure 9a and 9b).

[00158] Synthesis of 4-adamantyl-tetrahydro-2H-pyran-2-one (4)

[00159] To a stirred solution of toluene (20 mL), 3 (4.50 g, 0.02 mol), 2
10 (19.06 g, 0.19 mol), tributyltinhydride (6.30 g, 0.021 mol) is added, and the solution is heated to 100°C and AIBN (0.34 g, 10 mol%) is added, and refluxed for 2 h. The reaction mixture is cooled down to room temperature. A solution of 0.2 M potassium fluoride (100 mL) is added to the reaction mixture and vigorously stirred for overnight under room temperature, and a white solid residue
15 formed. The white solid residue is filtered off and the residue is washed with ethyl acetate (3 × 50 mL). The filtrate is diluted with ethyl acetate (50 mL) and water (50 mL). The resulting solution is extracted and the organic phase is washed with brine (2 × 50 mL). Ethyl acetate is removed under vacuo and the crude product is purified (hexane/ethyl acetate = 9/1) by silica gel column chromatography to
20 afford 3.19 g of 4 as a white solid. (62% yield). ¹H NMR (400 MHz, CDCl₃) δ: 4.38-4.33 (m, 1H), 4.21-4.15 (m, 1H), 2.58-2.52 (dd, 1H, J = 8 Hz, 16 Hz), 2.35-2.28 (dd, 1H, J = 12 Hz, 16 Hz), 1.98 (br, 3H), 1.87-1.84 (m, 1H), 1.72-1.44 (m, 12 H). ¹³C (150 MHz, CDCl₃) δ: 68.86 (s), 41.80 (s), 38.82 (s), 37.02 (s), 34.24 (s), 30.37 (s), 28.29 (s), 22.92 (s). HRMS (70 eV, EI): calcd for C₁₅H₂₁O₂ [M]⁺:
25 calcd 233.1620, found: 233.1627.

Synthesis of 4-adamantyl-pentane-1,5-di-ol (5)

[00160] To a stirred solution of dry THF (30 mL), 4 (1.02 g, 4.37 mmol) is added and the solution is cooled down to 0°C. The solution is stirred at 0°C for an
30 additional 10 min. Then lithiumaluminiumhydride (0.166 g, 4.37 mmol) is added portion wise to the solution at 0°C. The reaction mixture is stirred for 2 h at 0°C

under an inert atmosphere. A mixture of THF/water (5/1) is dropwise added to the reaction mixture at 0°C until gas production ceases. A 5% potassium hydroxide solution (10 mL) is added to the reaction mixture and is stirred vigorously at room temperature for 1 h. MgSO₄ (15 g) is added to the reaction mixture and is stirred
5 for 30 min. The white cake is filtered through a celite bed and the filtrate is washed with acetone (5 × 30 mL). The solvent was removed under vacuum and the crude product is purified by (hexane/acetone = 3/1) flash silica gel column chromatography to afford 1.0 g of 5 as a white solid. (85% yield) ¹H NMR (400 MHz, CDCl₃) δ: 4.05 (s, 2H), 3.49-3.38 (m, 4H), 1.79 (bs, 3H), 1.68-1.67 (m,
10 2H), 1.55-1.43 (m, 6H), 1.35 (br, 6H), 1.13-1.01 (m, 3H), 0.83-0.80 (1H); ¹³C (150 MHz, CDCl₃) δ: 58.00 (s), 37.40 (s), 35.32 (s), 33.09 (s), 31.22 (s), 27.44 (s), 24.48 (s); HRMS (70 eV, EI): calcd for C₁₅H₂₄O [M-H₂O]⁺: calcd 220.1933, found: 220.1920.

15 Synthesis of 4-adamantyl-1,5-dibromo-pentane (6)

[00161] To a stirred solution of 5 (2.20 g, 9.34 mmol) in DCM (200 mL), tetrabromomethane (12.38 g, 37.36 mmol) is added. The solution is stirred for 10 min at room temperature to achieve a clear solution. The reaction mixture is cooled down to 0°C and stirred for 10 min at 0°C. Triphenylphosphine (14.69 g,
20 56.04 mmol) is added to the reaction mixture at 0°C over a period of 30 min. The reaction mixture is allowed to warm to room temperature and is stirred for 20 h. The reaction mixture is quenched with distilled water (100 mL) and is diluted with DCM (100 mL). The reaction mixture is extracted with DCM and the combined organic layer is washed with brine (2 × 50 mL). The solvent is removed
25 under vacuum and is purified (hexane/ethyl acetate = 99/1) by silica gel column chromatography to afford 3.06 g of 6 as a colourless oil. (yield 92%) ¹H NMR (400 MHz, CDCl₃) δ: 3.44-3.36 (m, 4H), 1.76 (br, 3H), 1.67-1.65 (m, 2H), 1.56-1.44 (m, 6H), 1.33 (bs, 6H), 1.15-1.03 (m, 3H), 0.84-0.81 (m, 1H). ¹³C (150 MHz, CDCl₃) δ: 62.00 (s), 36.42 (s), 34.30 (s), 32.12 (s), 31.22 (s), 26.47 (s),
30 24.40 (s). HRMS (70 eV, EI): calcd for C₁₅H₂₃Br₂ [M]⁺: calcd 363.0224, found: 363.0237.

Synthesis of 4-adamantyl-1,5-diazido-pentane (7)

[00162] To a stirred solution of 6 (506 mg, 1.38 mmol) in DMF (5 mL) and water (0.7 mL), sodium azide (361 mg, 5.55 mmol) is added and the resulting reaction mixture is heated to reflux for 14 h. The reaction mixture is quenched
5 with water (20 mL) and extracted with ether (100 mL). Collective organic layer is washed with brine (3 × 30 mL) and dried over MgSO₄. The crude product is purified (hexane/ethyl acetate = 99/1) over silica gel column chromatography to afford 7 (286 mg, 84%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ: 3.37-3.21 (m, 4H), 1.99 (br, 3H), 1.92-1.84 (m, 2H), 1.72-1.50 (m, 12H), 1.28-1.24 (m,
10 2H), 0.84-0.80 (m, 1H). ¹³C (150 MHz, CDCl₃) δ: 51.35 (s), 43.19 (s), 39.45 (s), 37.03 (s), 35.54 (s), 28.79 (s), 28.44 (s). HRMS (70 eV, EI): calcd for C₁₅H₂₇N₄ [M-N₂]⁺: calcd 263.2157, found: 263.2168.

Synthesis of 2,2-dipropergyloxy-propane (10)

15 [00163] A flame dried two-neck round bottom flask is equipped with stirred bar and cooled down under an argon stream. Dry DCM (3 mL), 9 (4.4 g, 0.034 mol) and 8 (1.2 mL, 0.017 mol) are added under inert atmosphere at rt. The reaction mixture is cooled down to -78°C and trimethylsilyl trifluoromethanesulphonate (50 μL, 20 mol%) is added to the reaction mixture.
20 The solution is stirred at -78 °C for 2.5 h. After completion of the reaction pyridine (0.6 mL) is added. The reaction mixture is poured into saturated NaHCO₃ (20 mL) and extracted with ether (70 mL). The collective organic layer is washed with brine (2 × 25 mL). The crude product is purified (hexane/triethyl amine = 100/1) by silica gel column chromatography to afford 9 (1.5 g, 58%) as a
25 colourless oil ¹H NMR (400 MHz, CDCl₃) δ: 4.14 (d, 4H, J = 2 Hz), 2.39 (t, 2H, J = 2 Hz), 1.41 (s, 6H). ¹³C (150 MHz, CDCl₃) δ: 101.59 (s), 80.45 (s), 73.42 (s), 49.44 (s), 24.67 (s). HRMS (70 eV, EI): calcd for C₉H₁₃O₂ [M]⁺: calcd 152.0837, found 152.084.

Process for preparing complexes of pADK and cyclodextrin:

[00164] 1. The polyketal pendant polymer pADK is dissolved in a DMSO:Water mixture (2:8) at a concentration of 1mM [Ad], that is, 1mM concentration of the monomeric unit.

5 [00165] 2. The cyclodextrin or cyclodextrin derivatives are separately dissolved in water at 1mM concentration.

[00166] 3. The pADK and cyclodextrin solutions are then mixed in a 1:1 ratio to yield the final nanoparticle complexes comprised of the hydrophobic group to cyclodextrin in a 1:1 molar ratio.

10

[00167] Composition, analysis and mechanism of action of Polyadamantane-ketal and cyclodextrin conjugates:

[00168] The pADK polymer self-assembles with β -CD and its derivatives to form nanoparticles to improve the biodistribution and pharmacokinetic profile of the monomeric β -CD (Figure 12). The chemical structure of pADK is shown in Figure 9b, it is composed of a polyketal that has adamantane groups embedded in its backbone, flanked by triazole groups, and in the presence of acid degrades into low molecular weight diols and acetone, both of which are membrane permeable and rapidly excretable. pADK is designed to complex CD, generating a nanoparticle carrier with multiple copies of CD. However, after endocytosis and trafficking into the endosome, pADK hydrolyzes into small molecules, due to hydrolysis of the ketal linkage, and causes endosomal disruption via the colloid osmotic mechanism. Importantly, the cellular degradation products of pADK are an adamantane diol and acetone, both of which cause minimal toxicity due to their rapid excretion.

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[00169] The pADK:CD nanoparticles are assembled at room temperature by mixing them in a 1:1 molar ratio of the pendant adamantane group to CD.

30 [00170] To investigate the complex formation between pADK and β -CD, pADK microparticles are formulated and is encapsulated with rhodamine B

(Figure 12), and investigated if β -CD could stimulate release from these microparticles. pADK microparticles are suspended into solutions that contained 5 mM methyl- β -CD or PBS, and the release of rhodamine-B is measured. Complexation of pADK microparticles with methyl- β -CD should increase the hydrophilicity of the particles, and catalyse their disassembly leading to release of the dye. This can be attributed to the dissolution of surface pADK polymers on the microparticles, and the creation of water channels in the microparticles. Figure 12B demonstrates that methyl- β -CD stimulates the release of rhodamine-B from pADK microparticles. For example, in the presence of methyl- β -CD, pADK particles released their contents with a half-life of 15 hours, in contrast, in PBS, only 5% of the contents are released after 30 hours. Thus, methyl- β -CD dramatically accelerates the release of compounds from pADK microparticles, demonstrating that pADK forms complex with β -CD derivatives thus, acting as an efficient carrier for CD or its derivatives.

15

Example 4: Procedure for synthesis of Poly(vinyl alcohol)-(Adamantane)₆₅:cyclodextrin conjugates

Step 1: Synthesis of Ad-HB:

[00171] To a solution of 4-hydroxybenzaldehyde (610 mg, 5.0 mmol) in 5 mL dry THF is added Diisopropylamine (750 μ l, 4.306 mmol) under Argon atmosphere. The mixture is cooled with ice before drop wise adding a solution of Adamantane carbonyl chloride (1.5 g, 7.553 mmol) in 2.5 mL dry THF. After 6 hours, the THF is removed under reduced pressure. The residue is dissolved in 25 mL ether and then washed three times with 1 M Na₂CO₃ and one time with a saturated NaCl solution. The organic layer is dried over Na₂SO₄ and the solvent is removed via rotovap to yield a pale yellow solid. Yield: 1.196 g (84.2%). ¹H NMR (400 MHz, CDCl₃, δ): 9.99 (s, 1H, CHO), 7.91 (d, 2H, Ph-Ald), 7.23 (d, 2H, Ph-O), 2.09-2.05 (m, 9H, Ad), 1.81-1.74 (m, 6H, Ad).

30

Step 2: Synthesis of Ad- PVA:

[00172] Poly(vinyl alcohol) (MW = 27 kDa) (500 mg, 0.019 mmol) is added to 20 mL dry DMSO and purged with Argon. The suspension was then heated to 75°C. Once dissolved, Ad-HB (1.052 g, 3.895 mmol) is added followed by p-Toluenesulfonic acid monohydrate (200 mg, 1.051 mmol). The reaction is stirred for two days, after which it is cooled to room temperature, precipitated in bulk ether, filtered, and dried overnight. Yield: 1.190 g. Adamantane groups: ~65.

[00173] The number of adamantane groups are variable and can be as high as 200 – 300. In some instances, PEG can also be grafted on the backbone to increase blood circulation time. β -CD, SBE- β -CD, and HP- β -CD, are used in 1 CD: 1 Adamantane molar ratio to formulate the final complex

Step 3: Process for preparing complexes of Ad-PVA and cyclodextrin:

[00174] 1. The Ad-PVA pendant polymer is dissolved in a DMSO:Water mixture (1:1) at a concentration of 1mM [Ad], that is, 1mM concentration of the monomeric unit.

[00175] 2. The cyclodextrin or cyclodextrin derivatives are separately dissolved in water at 1mM concentration.

[00176] 3. The Ad-PVA and cyclodextrin solutions are then mixed in a 1:1 ratio to yield the final nanoparticle complexes comprised of the hydrophobic group to cyclodextrin in a 1:1 molar ratio.

Example 5: Procedure for synthesis of *PEG-G-(K-Adamantane)₉*: cyclodextrin conjugates

Step 1: Synthesis of CBz-(GK)₉:

[00177] The polypeptide of sequence Glycine-(Lysine)₉ peptides are synthesized using an Fmoc-based, solid-phase strategy on the Wang resin. The peptide is purified to homogeneity by reverse-phase HPLC and characterized by ¹H NMR, MS, and HPLC. The synthesized peptide is produced with a CBz-protected N-terminus glycine.

Step 2: Synthesis of CBz-[G(K-Adamantane)]₉:

[00178] 100mg (0.055mmol) of the polypeptide from the previous step is dissolved in 5ml dry DMSO under N₂. To this solution, 0.15mL (0.825 mmol, 1.6eq) of diisopropylethylamine is added and stirred, followed by addition of 22 mg (0.11mmol, 2eq) of adamantane carbonyl chloride. The reaction mixture is stirred overnight under N₂ atmosphere after which it is dialyzed exhaustively against DMSO (thrice), followed by deionized water (thrice) using a 2000 MWCO dialysis membrane to remove any unreacted adamantane carbonyl chloride and base. The dialyzed sample is then lyophilized to afford a dry powder.

10 The product is then analyzed by ¹HNMR, HPLC, and GPC.

Step 3: Synthesis of PEG-[G(K-Adamantane)]₉:

[00179] The CBz group is deprotected using conventional catalytic hydrogenation in presence of Pd/C followed by purification by dialysis to afford the deprotected Ad modified peptide. This is then reacted with hetero bifunctional PEG modified with the NHS group at one terminus in presence of base to afford the final PEGylated peptide which is purified by dialysis as mentioned before. The final product is analyzed by ¹H NMR, HPLC, and GPC.

15

20 Step 4: Process for preparing complexes of PEG-[G(K-Adamantane)]₉ and cyclodextrin:

[00180] 1. The PEG-[G(K-Adamantane)]₉ pendant polypeptide is dissolved in water mixture at a concentration of 1mM [Ad], that is, 1mM concentration of the monomeric unit.

25 [00181] 2. The cyclodextrin or cyclodextrin derivatives are separately dissolved in water at 1mM concentration.

[00182] 3. The polypeptide and cyclodextrin solutions are then mixed in a 1:1 ratio to yield the final nanoparticle complexes comprised of the hydrophobic group to cyclodextrin in a 1:1 molar ratio.

Example 6: Procedure for synthesis of PEG-Glycine-(Lysine-Cholesterol)₉ and cyclodextrin conjugates:

[00183] Step 1: Synthesis of CBz-(GK)₉:

[00184] The polypeptide of sequence Glycine-(Lysine)₉ is synthesized as
5 mentioned in the previous Example.

[00185] Step 2: Synthesis of CBz-[G(K-Cholesterol)]₉:

[00186] 100mg (0.055mmol) of the polypeptide from the previous step is
dissolved in 5ml dry DMSO under N₂. To this solution, 0.15mL (0.825 mmol,
10 1.6eq) of diisopropylethylamine is added and stirred, followed by addition of 50
mg (0.11mmol, 2eq) of cholesteryl chloroformate. The reaction mixture is stirred
overnight under N₂ atmosphere after which it is dialyzed exhaustively against
DMSO (thrice), followed by deionized water (thrice) using a 2000 MWCO
dialysis membrane to remove any unreacted cholesteryl chloroformate and base.
15 The dialyzed sample is then lyophilized to afford a dry powder. The product is
then analyzed by ¹H NMR, HPLC, and GPC.

[00187] Step 3: Synthesis of PEG-[G(K-Cholesterol)]₉:

[00188] The PEGylated peptide is synthesized in a similar manner to the
20 PEG-G-(K-Adamantane)₉ as described in the previous Example, and analyzed
accordingly.

[00189] Step 4: Process for preparing complexes of PEG-G-(K-
Cholesterol)₉ and cyclodextrin:

25 [00190] 1. The PEG-[G(K-Cholesterol)]₉ pendant polypeptide is dissolved
in water mixture at a concentration of 1mM [Chol], that is, 1mM concentration of
the monomeric unit.

[00191] 2. The cyclodextrin or cyclodextrin derivatives are separately
dissolved in water at 1mM concentration.

[00192] 3. The polypeptide and cyclodextrin solutions are then mixed in a 1:1 ratio to yield the final nanoparticle complexes comprised of the hydrophobic group to cyclodextrin in a 1:1 molar ratio.

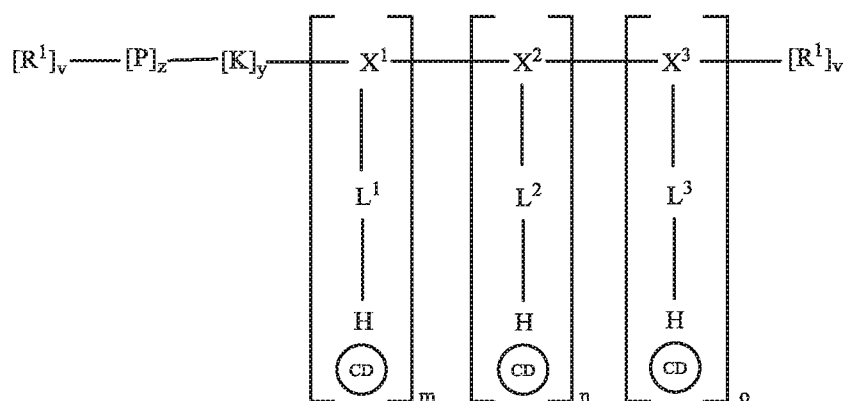
5 [00193] Additional embodiments and features of the present disclosure will be apparent to one of ordinary skill in art based upon description and examples provided herein. However, the examples below should not be construed to limit the scope of the present disclosure.

10 [00194] The foregoing description of the specific embodiments will so fully reveal the general nature of the embodiments herein that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without departing from the generic concept, and, therefore, such adaptations and modifications should and are intended to be comprehended
15 within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the phraseology or terminology employed herein is for the purpose of description and not of limitation. Therefore, while the embodiments in this disclosure have been described in terms of preferred embodiments, those skilled in the art will recognize that the embodiments herein can be practiced with
20 modification within the spirit and scope of the embodiments as described herein.

[00195] Thus, the present disclosure introduces pendant guest-host complexes, corresponding methods and applications wherein said complexes possess improved properties such as, prolonged duration of action along with
25 efficacy for removing cholesterol from the cells/treating lipid storage disorders.

WHAT IS CLAIMED IS:

1. A compound comprising the following structure:



5 wherein,

R^1 is independently 2-hydroxy propyl, 1-hydroxy methyl, OH, CO_2H or NH_2 ;

P is a polymer;

X^1 , X^2 and X^3 are each backbone moieties;

10 L^1 , L^2 , L^3 and K are each linker moieties, wherein each of L^1 , L^2 and L^3 may be present or absent;

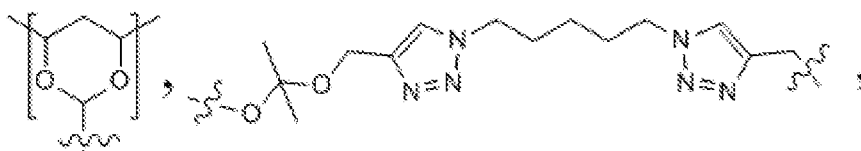
H is host moiety attached directly to the backbone moiety or via the linker moiety;

15 CD is a cyclodextrin, or a derivative thereof; wherein CD is non-covalently conjugated to H;

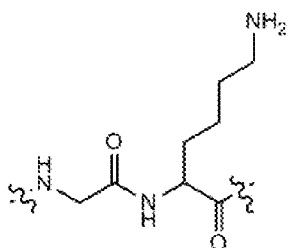
m, n and o are each independently from 0 to 1000, wherein at least one of m, n and o is at least 4; and

v, z and y are each independently 0 to 500.

2. The compound of claim 1, wherein each instance of X¹, X² and X³ is independently selected from C₁-C₄hydroxyalkyl, (C₁-C₄ alkyl)-O-(C₁-C₄ alkyl)-O-(C₁-C₄ alkyl), (C₁-C₄ alkyl)-O-(C₁-C₄ alkyl), peptide, Gly-Lys,

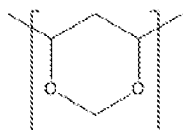


5



or an amino acid;

wherein when X¹ or X² or X³ is independently



10

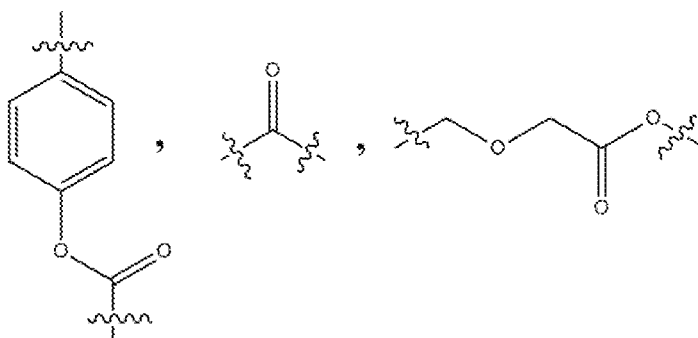
the linker moiety or hydrophobic moiety is directly attached to C1 carbon of cyclic ketal moiety; and

wherein when X¹ or X² or X³ is independently



the linker moiety or hydrophobic moiety is directly attached to C3 carbon of pentane chain.

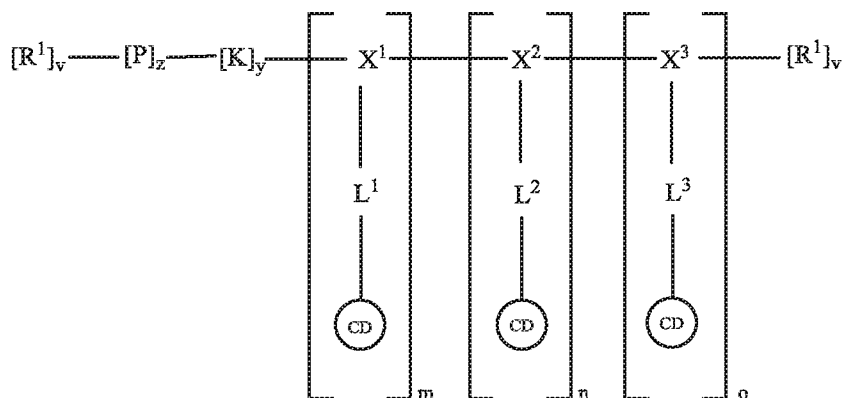
3. The compound of claim 1, wherein polymer is selected from poly vinyl alcohol, polyketal or polyethylene glycol.
4. The compound of claim 1, wherein each of L^1 , L^2 , L^3 and K independently is selected from an alkyl ester, an alkyl amide, an alkyl carbonate, an alkyl carbamate,



- or Ar^1 , wherein Ar^1 is an optionally substituted 5- or 6- membered aryl, heteroaryl comprising 1, 2, 3 or 4 heteroatoms individually selected from N, O, and S.
5. The compound of claim 4, wherein Ar^1 is triazole.
6. The compound of claim 1, wherein the cyclodextrin or a derivative thereof is selected from α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin, derivatives thereof, or combinations thereof.

7. The compound of claim 6, wherein the cyclodextrin or a derivative thereof is selected from hydroxyalkyl- α -cyclodextrin, hydroxyalkyl- β -cyclodextrin, hydroxyalkyl- γ -cyclodextrin, derivatives thereof, or combinations thereof.
8. The compound of claim 7, wherein alkyl group in hydroxyalkyl- α -cyclodextrin, hydroxyalkyl- β -cyclodextrin, hydroxyalkyl- γ -cyclodextrin or their derivatives is selected from C₁-C₁₀ linear alkyl, C₁-C₁₀ branched alkyl or C₁-C₁₀ cycloalkyl, each having one or more optional substituents.
9. The compound of claim 1, wherein H is selected from cycloalkyl, heterocycloalkyl, aryl or heterocycloaryl.
10. The compound of claim 9, wherein H is adamantane or noradamantane.
11. The compound of claim 1, wherein H is cholesterol.
12. The compound of claim 1, wherein m, n or o is from 3 to 30.
13. The compound of claim 1, wherein m, n or o is from 10 to 100.
14. The compound of claim 13, wherein m, n or o is from 15 to 65.
15. The compound of claim 14, wherein m, n or o is from 20 to 30.
16. The compound of claim 14, wherein m, n or o is from 50 to 65.

17. A compound comprising the following structure:



wherein

5 R^1 is independently 2-hydroxy propyl, 1-hydroxy methyl, OH, CO_2H or NH_2 ;

P is a polymer;

X^1 , X^2 and X^3 are each backbone moieties;

10 L^1 , L^2 , L^3 and K are each linker moieties, wherein each of L^1 , L^2 and L^3 may be present or absent, provided at least one of L^1 , L^2 and L^3 is present;

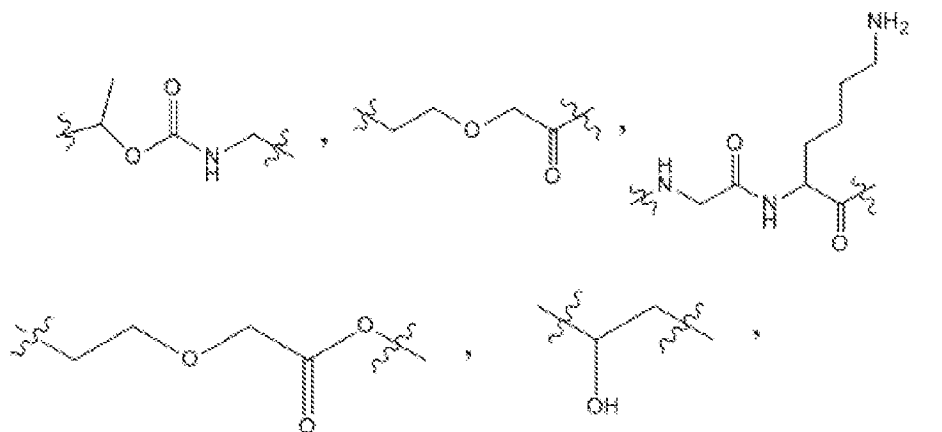
CD is a cyclodextrin, or a derivative thereof, wherein each CD is covalently attached to respective L^1 , L^2 , L^3 ; and

m, n and o are each independently from 0 to 1000, wherein at least one of m, n and o is at least 4; and

15 v, z and y are each independently 0 to 500.

18. The compound of claim 17, wherein each instance of X^1 , X^2 and X^3 is independently selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 hydroxyalkyl,

(C₁-C₄ alkyl)-O-(C₁-C₄ alkyl)-O-(C₁-C₄ alkyl), (C₁-C₄ alkyl)-O-(C₁-C₄ alkyl),
alkyl ester, peptide, Gly-Lys,



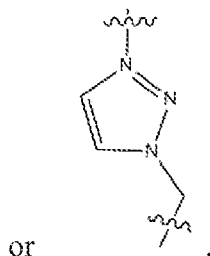
or an amino acid; wherein when X¹ or X² or X³ is independently Gly-Lys,
5 the linker moiety is attached to omega amino group of Lysine.

19. The compound of claim 17, wherein polymer is selected from poly vinyl
alcohol, polyketal or polyethylene glycol.
20. The compound of claim 17, wherein the cyclodextrin or a derivative thereof is
selected from α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin, derivatives
10 thereof, or combinations thereof.
21. The compound of claim 20, wherein the cyclodextrin or a derivative thereof is
selected from hydroxyalkyl- α -cyclodextrin, hydroxyalkyl- β -cyclodextrin,
hydroxyalkyl- γ -cyclodextrin, derivatives thereof, or combinations thereof.
22. The compound of claim 21, wherein alkyl in hydroxyalkyl- α -cyclodextrin,
15 hydroxyalkyl- β -cyclodextrin, hydroxyalkyl- γ -cyclodextrin or their derivatives
selected from C₁-C₁₀ linear alkyl, C₁-C₁₀ branched alkyl or C₁-C₁₀ cycloalkyl,
each having one or more optional substituents.

23. The compound of claim 17, wherein each of L¹, L² and L³ independently is selected from an alkyl, an alkyl ester, an alkyl amide, an alkyl carbonate, an alkyl carbamate, or Ar¹, wherein Ar¹ is an optionally substituted 5- or 6-membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms individually selected from N, O, and S.

5

24. The compound of claim 23, wherein Ar¹ is an optionally substituted triazole



25. The compound of claim 17, wherein m, n or o is from 3 to 30.

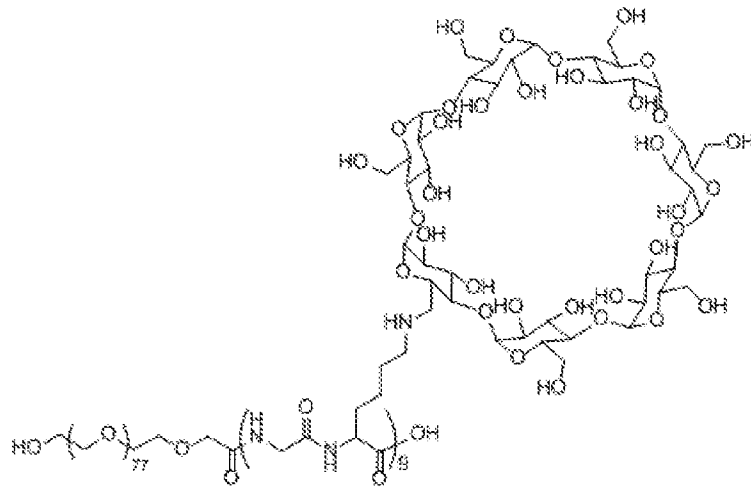
26. The compound of claim 25, wherein m, n or o is from 10 to 100.

10 27. The compound of claim 26, wherein m, n or o is from 15 to 65.

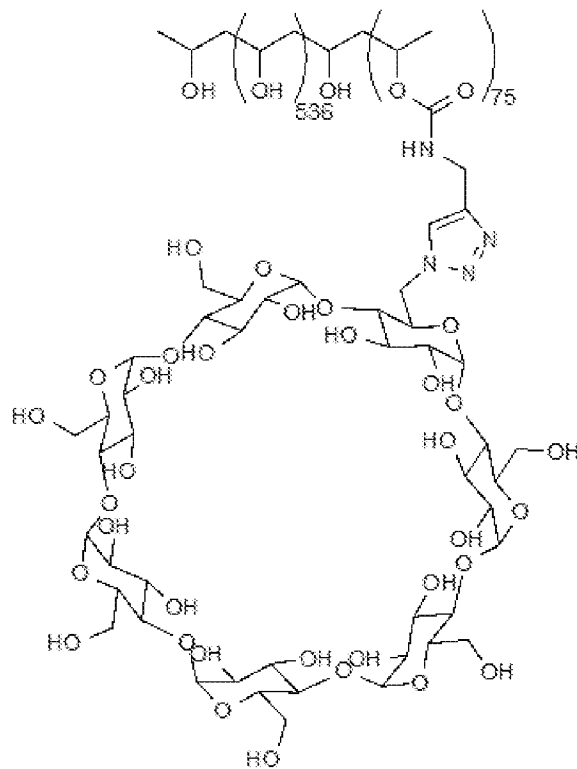
28. The compound of claim 26, wherein m, n or o is from 20 to 30.

29. The compound of claim 27, wherein m, n or o is from 50 to 65.

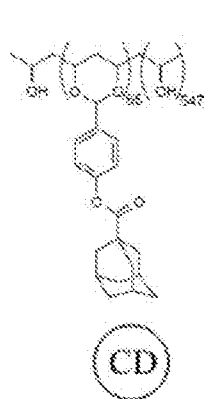
30. A compound of claim 1 or claim 17, wherein the compound is selected from:



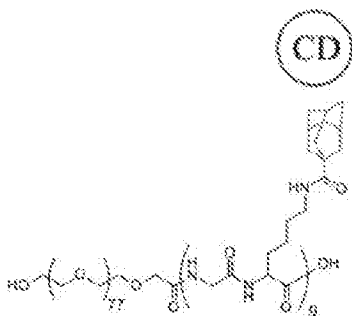
PEG-[Glycine-(Lysine-β-CD)]₉



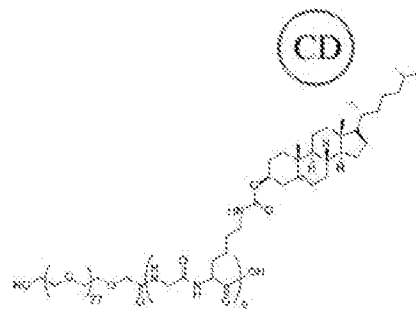
Poly(vinyl alcohol)-trz-(β-CD)₇₅



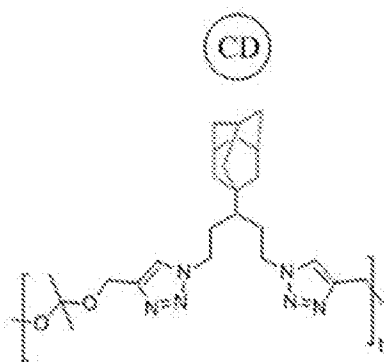
**Poly(vinyl alcohol)-
(Adamantane)₆₅
complexed with CD**



**PEG-[Glycine-(Lysine-
Adamantane)]₉
complexed with CD**



**PEG-[Glycine-(Lysine-
Cholesterol)]₉
complexed with CD**

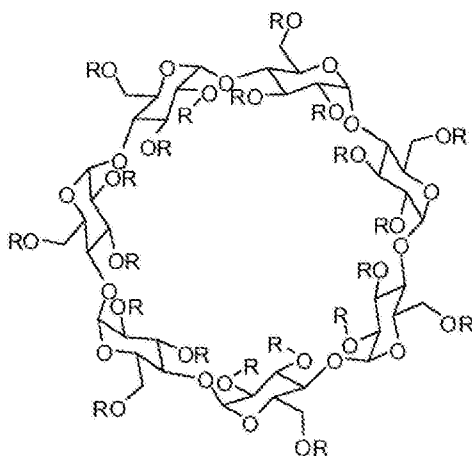


wherein 't' ranges from 5 to 500

**pADK polymer
complexed with CD**

31. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or a pharmaceutical excipient and a compound of any one of claims 1-30.
- 5 32. The pharmaceutical composition of claim 31, further comprising a therapeutically active agent.

33. A method of treating a disease or a condition associated with abnormal NPC1 and/or NPC2 protein production, comprising administering to a subject in need thereof a compound of any one of claims 1-30, or a composition of claim 31.
- 5 34. A method of treating lipid storage disorder comprising administering to a subject in need thereof a compound of any one of claims 1-30, or a composition of claim 31.
35. A method of treating Niemann-Pick disease, comprising administering to a subject in need thereof a compound of any one of claims 1-30, or a
10 composition of claim 31.
36. The compound of any one of claims 1-30, where the compound has an elimination half-life of from about 6 hours to about 24 hours.
37. The pharmaceutical composition of claim 32, wherein the bioavailability of the therapeutically active agent is improved.



R=H, β-Cyclodextrin;
 R= -CH₂CH(OH)CH₃, Hydroxy propyl β-Cyclodextrin;
 R = -(CH₂)₄SO₃Na, Sulfobutylether β-Cyclodextrin

Figure 1

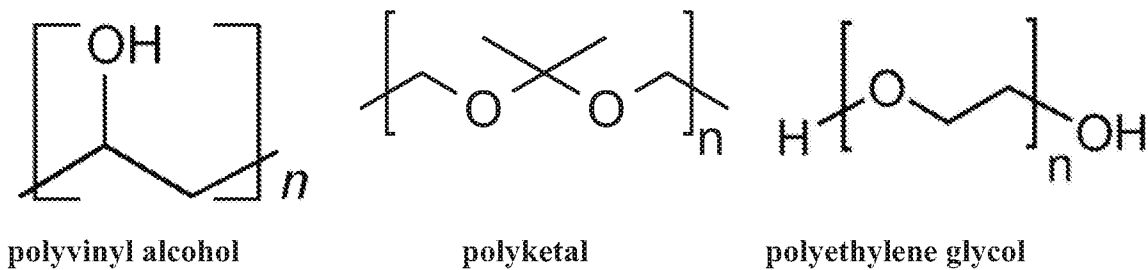


Figure 2

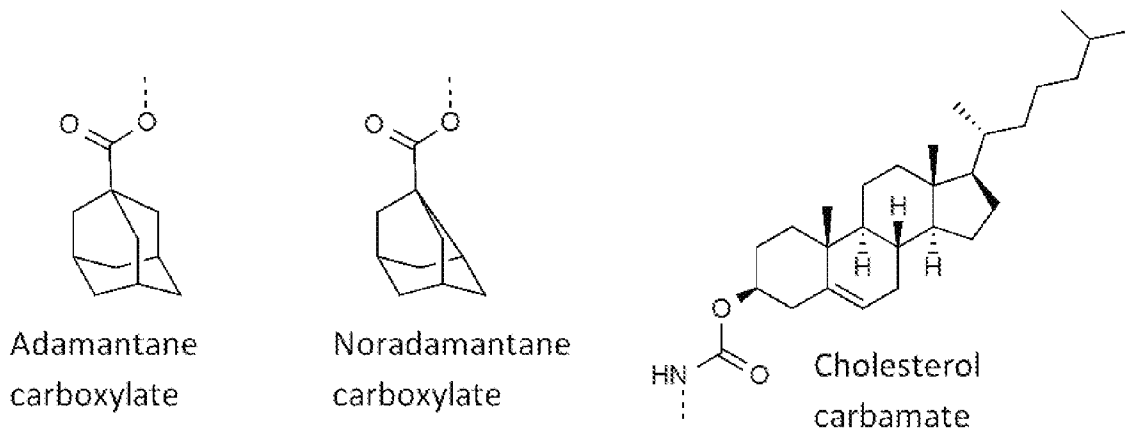


Figure 3

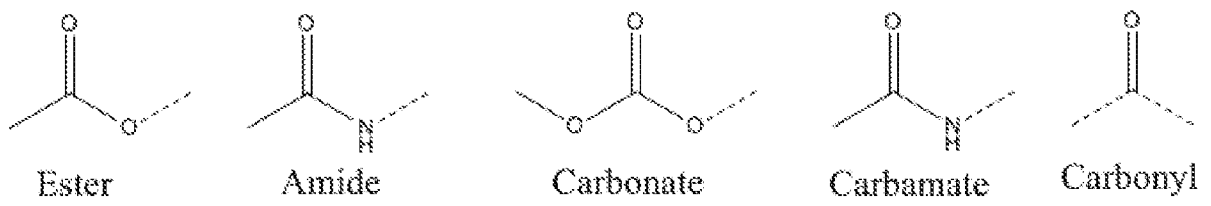


Figure 4

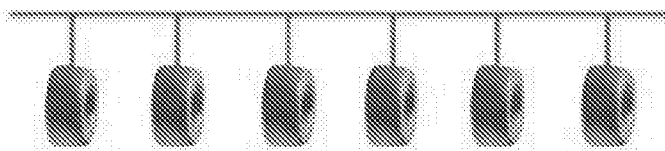


Figure 5

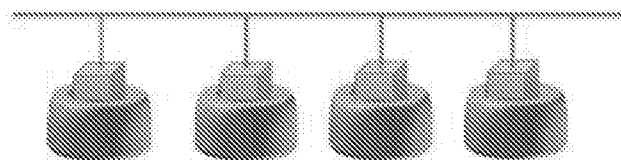
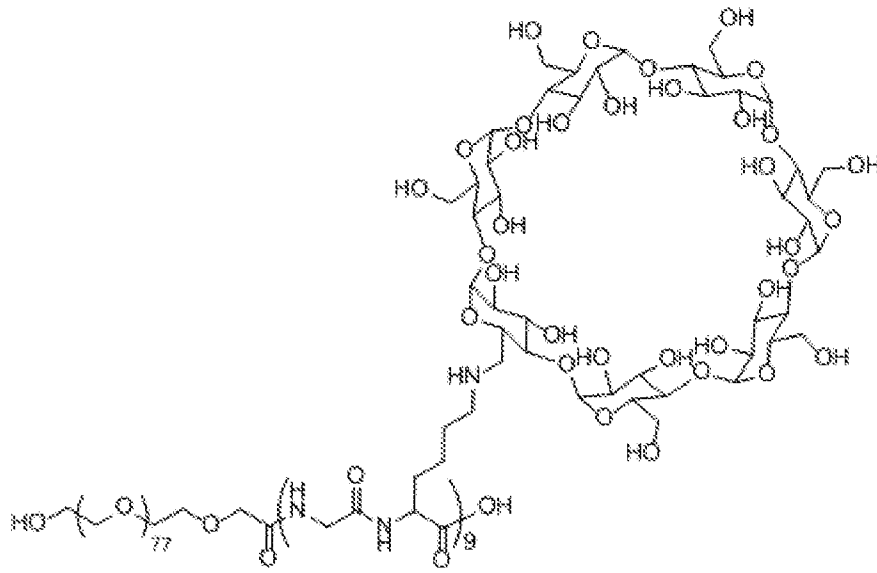
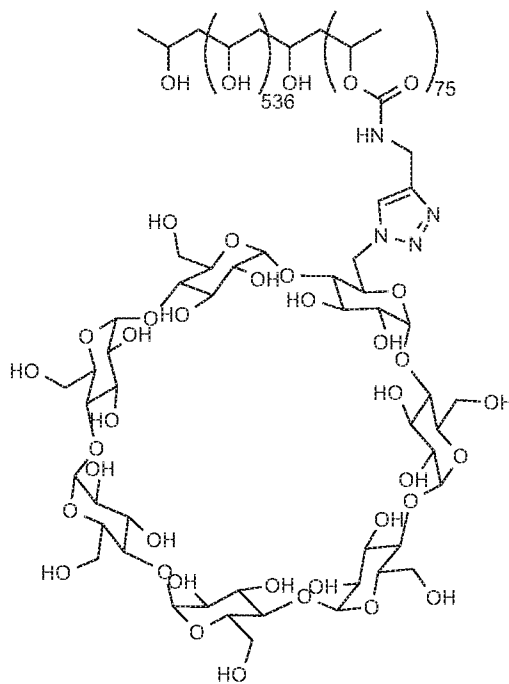


Figure 6



PEG-[Glycine-(Lysine-β-CD)]₉



Poly(vinyl alcohol)-trz-(β-CD)₇₅

Figure 7

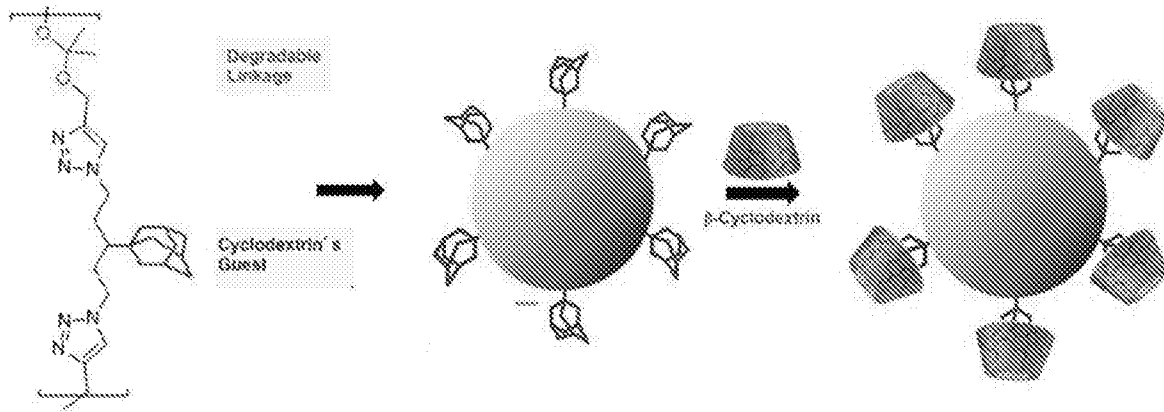
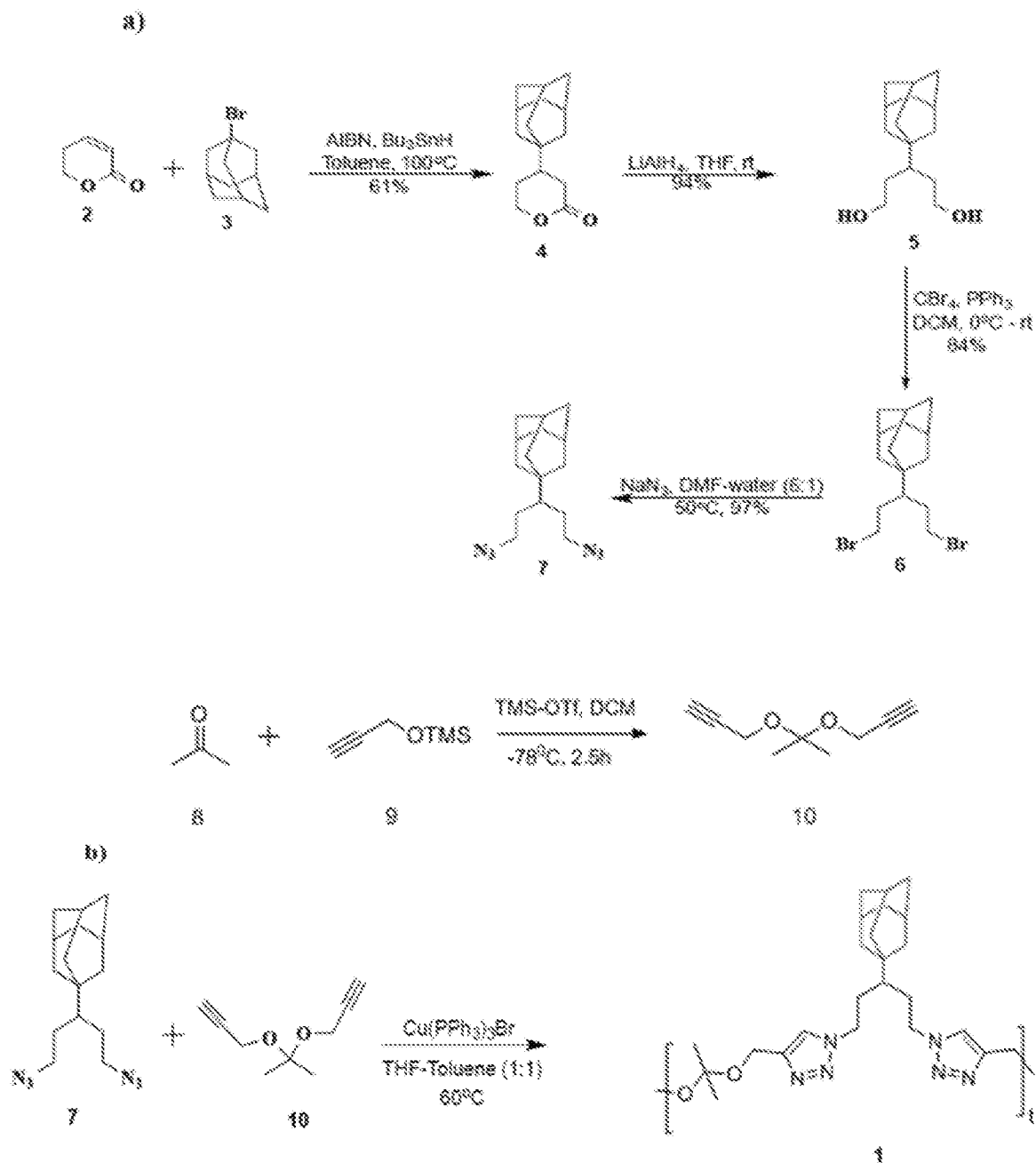


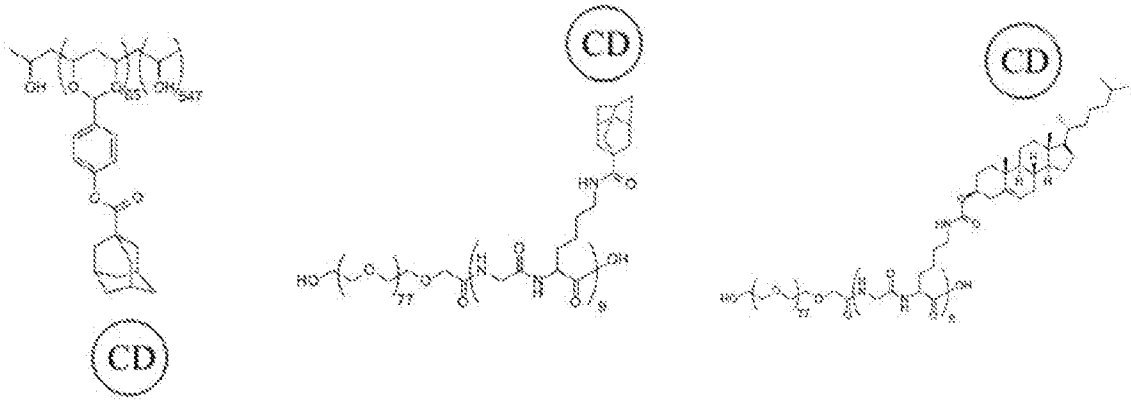
Figure 8



wherein 't' ranges from 5 to 500; and

molecular weight ranges from 3000 to 300000.

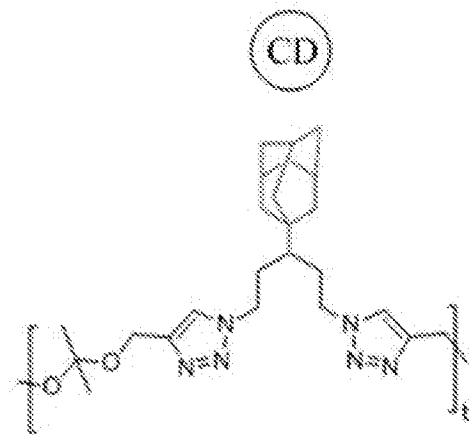
Figure 9: Schemes for synthesis of (a) 2,2-dipropergyloxy-propane[10] (b) pADK polymer[1].



**Poly(vinylalcohol)-
(Adamantane)₆₅
complexed with CD**

**PEG-[Glycine-(Lysine-
Adamantane)]₉
complexed with CD**

**PEG-[Glycine-(Lysine-
Cholesterol)]₉
complexed with CD**



wherein 't' ranges from 5 to 500

**pADK polymer
complexed with CD**

Figure 10

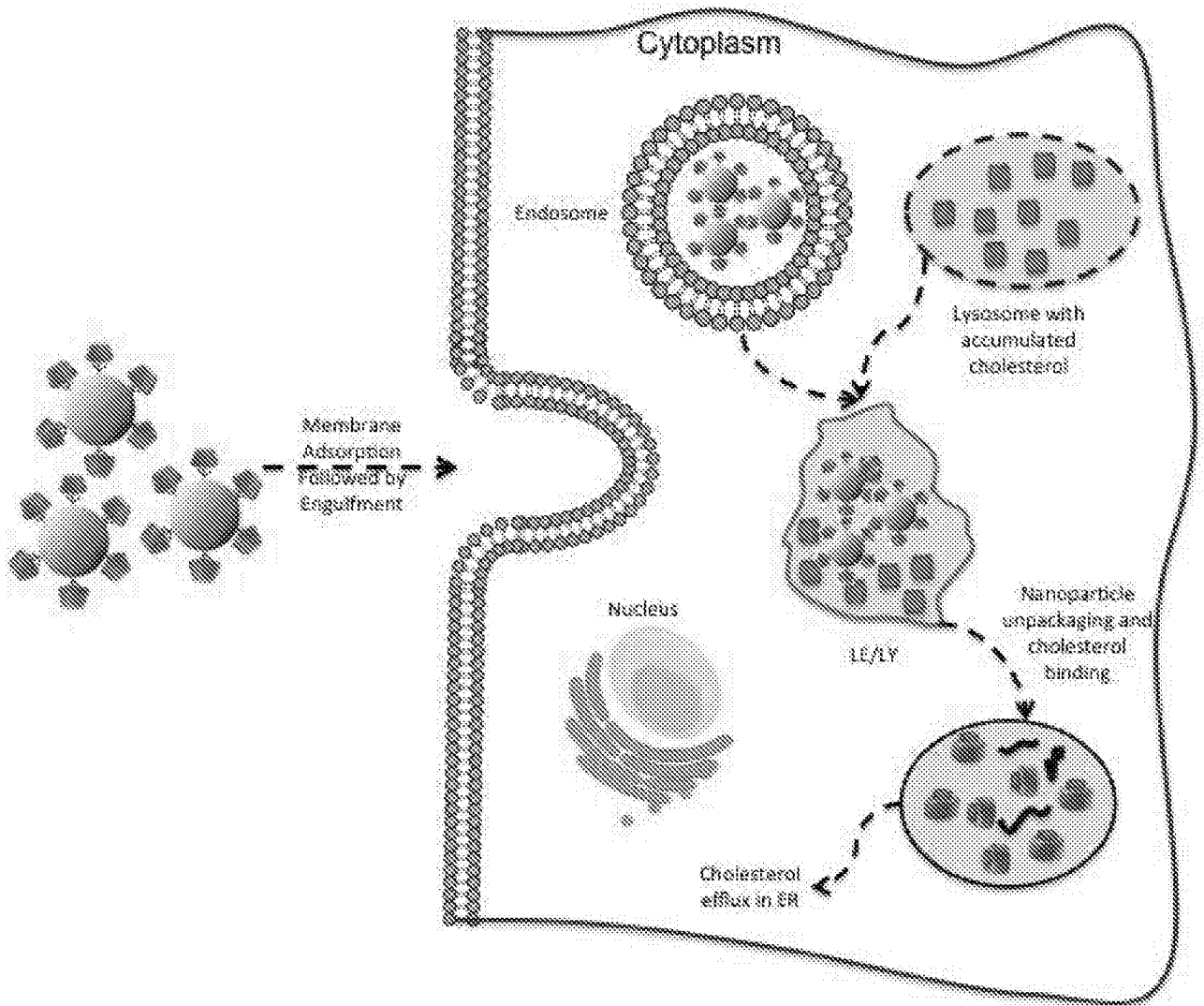
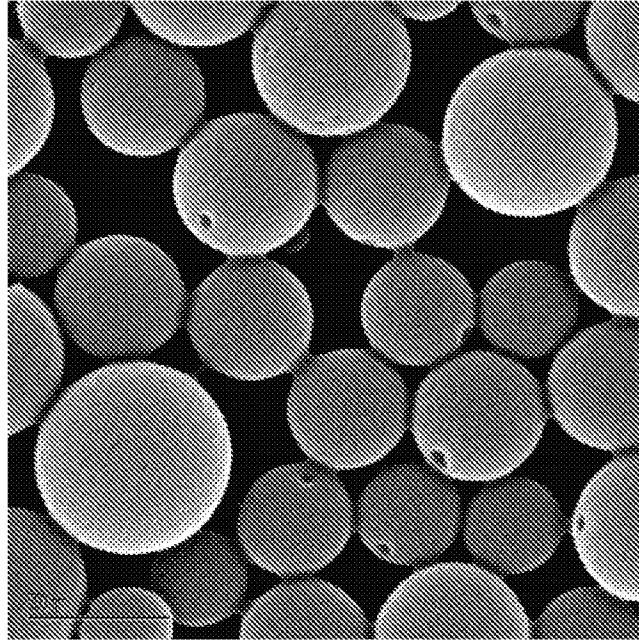


Figure 11

(A)



(B)

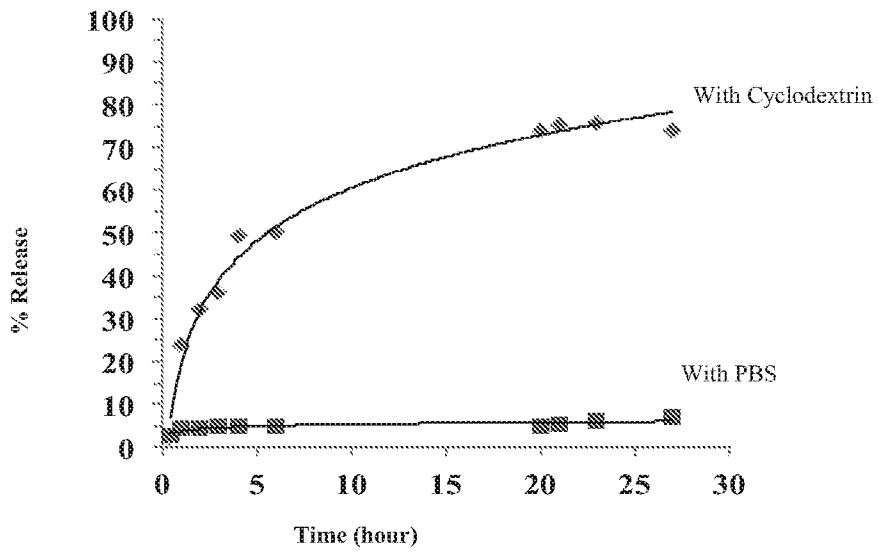


Figure 12

INTERNATIONAL SEARCH REPORT

International application No PCT/IB2016/054086

A. CLASSIFICATION OF SUBJECT MATTER INV. C08B37/16 C08L5/16 A61K47/40 ADD.				
According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C08B C08L A61K				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, CHEM ABS Data, COMPENDEX, EMBASE, WPI Data				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	US 2013/261168 A1 (THOMPSON DAVID H [US] ET AL) 3 October 2013 (2013-10-03)	1-16, 30-32, 36, 37		
Y	the whole document	33-35		
A	in particular: abstract; [0006]-[0009], [0039]-[0062], [0076]-[0083] and [0090]-[0096]; claims 1-20; figures 1-27; examples ----- -/--	17-29		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"><input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.</td> <td style="width: 50%; border: none;"><input checked="" type="checkbox"/> See patent family annex.</td> </tr> </table>			<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/> See patent family annex.
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/> See patent family annex.			
* Special categories of cited documents : <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"> "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed </td> <td style="width: 50%; border: none;"> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family </td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family			
Date of the actual completion of the international search	Date of mailing of the international search report			
25 October 2016	03/11/2016			
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Ferreira, Roger			

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2016/054086

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ADITYA KULKARNI ET AL: "Development of a Low Toxicity, Effective pDNA Vector Based on Noncovalent Assembly of Bioresponsive Amino-[beta]-cyclodextrin:Adamantane-Poly(vinyl alcohol)-Poly(ethylene glycol) Transfection Complexes", BIOCONJUGATE CHEMISTRY., vol. 23, no. 5, 2 May 2012 (2012-05-02), pages 933-940, XP055310662, US ISSN: 1043-1802, DOI: 10.1021/bc2005158	1-16, 30-32, 36,37
Y	the whole document	33-35
A	in particular: abstract; experimental procedures; results and discussion; figures 1-6	17-29

X	ADITYA KULKARNI ET AL: "Effect of Pendant Group on pDNA Delivery by Cationic-[beta]-Cyclodextrin:Alkyl-PVA-PEG Pendant Polymer Complexes", BIOMACROMOLECULES, vol. 15, no. 1, 2 December 2013 (2013-12-02), pages 12-19, XP055311053, US ISSN: 1525-7797, DOI: 10.1021/bm401096v	1-16, 30-32, 36,37
Y	the whole document	33-35
A	in particular: abstract; experimental section; results and discussion; figures 1-5	17-29

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