

LIPID-POLYMER HYBRID NANOPARTICLES

TECHNICAL FIELD

[0001] The present invention relates to a lipid polymer hybrid nanoparticles and pharmaceutical composition containing lipid-polymer hybrid nanoparticles along with a method to prepare such nanoparticles and nanoparticle containing compositions. Specifically, the invention is related to nanoparticles for pharmaceutical compositions, and coating compositions for medical devices, drug delivery, and diagnosis.

BACKGROUND

[0002] Nanoparticle-based drug delivery system provide multiple benefits over the conventional drug delivery systems. The main benefits are control over drug release in the tissue, higher drug transfer for a particular amount of drug used in drug delivery system, longer drug retention in the nanoparticles which in turn increases longer drug supply to the tissues and lower drug washout in the biological fluids. Biodegradable polymers are preferred choice to be used as a base material to prepare nanoparticles for implantable medical devices. They not only aid in controlling the drug release but goes out of the living being's body over a period of time after degradation. Lipids help in forming micelles which is a basis of forming the nanoparticles and they also help in stabilizing the dispersions in the process of nanoparticle formation.

[0003] The present disclosure is focused on utilizing properties of lipids and biodegradable polymers and to develop unique lipid-polymer hybrid nanoparticles to overcome some drug delivery challenges related to drug release control, drug retention and loss of drug during traction. Hence, it is an objective of this invention to provide lipid polymer hybrid nanoparticles which achieve controlled drug release over a longer period of time, reduced drug loss due to blood flow, increased drug transfer and retention in the biological tissues after application.

[0004] Also, it is another objective of this invention to provide a method to prepare above mentioned lipid polymer hybrid nanoparticles and compositions having above mentioned properties.

[0005] The above aspects are further illustrated in the figures and described in the corresponding description below. It should be noted that the description and figures merely illustrate principles of the present invention. Therefore, various arrangements that encompass the principles of the present invention, although not explicitly described or shown herein, may be devised from the description, and are included within its scope.

10 **BRIEF DESCRIPTION OF ACCOMPANYING DRAWINGS**

[0006] The detailed description is described with reference to the accompanying figures.

FIG. 1 illustrates a schematic diagram of a pharmaceutical agent carrying lipid-polymer hybrid nanoparticle, according to an embodiment of the present invention.

FIG. 2 illustrates an in-vitro drug release profile of lipid-polymer hybrid nanoparticles comprising a pharmaceutical agent, according to an embodiment of the present invention.

FIG. 3 illustrates an ex-vivo drug transfer and retention profile of a pharmaceutical agent carrying, two different lipid-polymer hybrid nanoparticles in tissue over 24 hours duration, according to two embodiments of the present invention.

FIG. 4 illustrates an ex-vivo drug transfer and retention profile of a pharmaceutical agent carrying lipid-polymer hybrid nanoparticles containing coating composition in tissue over 72 hours duration, according to an embodiment of the present invention and its comparison with similar profile of a competitor's product (commercially available).

DESCRIPTION OF THE INVENTION

[0007] The present disclosure along with the disclosed drawings explains the presented embodiments but does not intend to be the only embodiments constructed from the disclosure. The disclosure sets forth the application or utility
5 of the embodiments and sequence of steps to achieve the embodiments. The same application or utility and sequence of steps can be adopted by different embodiments.

[0008] As described herein, any concentration range, percentage range, ratio range or integer range is to be understood to include the value of any integer
10 within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated.

[0009] As used herein, the term “pharmaceutical agent” refers to any biologically active compound or a drug molecule that can be used in the formulation or a composition that is suitable for administration in mammals
15 including humans.

[0010] As used herein, the term “nanoparticle” refers to a lipid-polymer hybrid nanoparticle with a nanosized structure in which at least one or more dimension (s) (length, width, or thickness) of the nanoparticle is in the nanometer size range. The nanoparticles can be of any shape such as spherical, oval, disc-shaped,
20 cylindrical or hexagonal-shaped.

[0011] As per the present invention and as used herein, the term “primary excipient” refers to the phospholipid-based peripheral area in the structure of the nanoparticle where the pharmaceutical agent is densely accumulated in the range of 51 wt.% to 99 wt. % of the total pharmaceutical agent, specifically in the range
25 of 70 wt.% to 97 wt. % of the total pharmaceutical agent and more specifically, in the range of 80 wt.% to 95 wt. % of the total pharmaceutical agent.

[0012] As per the present invention and as used herein, the term “secondary excipient” refers to the biodegradable polymeric core area in the structure of the

nanoparticle where amount of the pharmaceutical agent is lower as compared to the primary excipient.

[0013] According to an embodiment of the present disclosure, a nanoparticle is a micelle that comprises a lipid shell enclosing a polymeric core, wherein the lipid shell comprises at least one amphiphilic lipid, and the polymeric core comprises at least one biodegradable polymer, at least one pharmaceutical agent and, optionally, at least one surfactant. Further, the lipids may be attached with functionalized moieties containing organic functional groups, specifically functionalized with polyethylene glycol (PEG). The polymeric core has uniformly distributed biodegradable polymer. However, the pharmaceutical agent may or may not be uniformly dispersed in the biodegradable polymer matrix.

[0014] The nanoparticles as per present disclosure are designed to store majority part or major weight percent of the pharmaceutical agent on the periphery of the nanoparticle, specifically on inner side of the periphery. The pharmaceutical agent is densely stored closest to the periphery and its concentration decreases in the direction of the center of the nanoparticle. Hence, comparatively, minor part or weight percent of the pharmaceutical agent is present towards the center of the core or distributed in the main biodegradable polymeric core. Hence, on exposure of such nanoparticles to a tissue, the pharmaceutical agent entrapped or concentrated on the periphery of the nanoparticle becomes primary and an easily available source of the pharmaceutical agent. Hence, the periphery, specifically inner periphery, of the nanoparticles becomes the primary excipient part in the nanoparticle whereas the polymeric core containing minority part of the pharmaceutical agent becomes the secondary excipient part in the nanoparticle. This nanoparticle design is achieved using a combination of solvent and antisolvent for a specific pharmaceutical agent, along with other basic raw materials, while forming the nanoparticles. Also, hydrophobic, lipophilic nature of the pharmaceutical agent is utilized in designing such nanoparticles.

[0015] According to the present invention, the lipid shell of the nanoparticle comprises at least one amphiphilic lipid selected from, but is not limited to,

phospholipids, lipid-polyethyleneglycol conjugate, cholesterol, PEGylated phospholipids, cationic lipids, soya phospholipids, egg phospholipids, lecithin, DC-cholesterol, chemically modified cholesterol, cholesterol conjugate or a combination thereof.

5 **[0016]** According to the present invention, the micellar core of the nanoparticle comprises at least one biodegradable polymer selected from, but is not limited to, polymers of L-lactide, Glycolide or combinations of thereof, poly(L-lactide-co-caprolactone) (PLCL), poly dl lactide (PDLLA), poly dl lactide-co-glycolide (PLGA), poly dl lactide-co-caprolactone (PLLCL),
10 poly(hydroxybutyrate), polyorthoesters, poly anhydrides, poly(glycolic acid), poly(glycolide), poly(L-lactic acid), poly(L-lactide), poly(D-lactic acid), poly(D-lactide), poly(caprolactone), poly(trimethylene carbonate), polyester amide, polyesters, polyolefins, polycarbonates, polyoxymethylenes, polyimides, polyethers, and copolymers and combination thereof.

15 **[0017]** According to the present invention, for biodegradable polymer, a solvent having Hansen solubility parameter value in the range of 18 to 25 and the solvent is selected from, but not limited to, Acetone, Acetonitrile, Tetrahydrofuran, Nitromethane, chloroform, Dichloromethane, Ethyl acetate.

20 **[0018]** According to the present invention, for biodegradable polymer, an anti-solvent having Hansen solubility parameter value that should not be in range of 18-25 and the anti-solvent is selected from, but not limited to, methanol, ethanol, Allyl alcohol, Ethanolamine, Hexane, Heptane, Cyclohexane, 1-octanol, Pentane, Xylene. Specifically, Hansen solubility parameter value of the anti-solvent is in range of 10-15 or in range of 25-40. More specifically, Hansen
25 solubility parameter value of the solvent is in range of 25-40. Further, a volume percentage ratio of solvent and antisolvent mixture varies in range of 0.01 to 3.5.

30 **[0019]** According to one embodiment of the present disclosure, the pharmaceutical agent is selected from but not limited to anti-cancer drug, antiproliferation drug, anti-restenosis drugs, Neurolytic agents, Quaternary ammonium salts, Sodium Channel Blockers, Anesthetics, Amino Acids, Amines,

Calcium Channel Blockers, Diuretics, Vasovasorum Constrictors, Neurotransmitter Chemicals, Venom, Sclerosant Agents, Anti-Nerve Growth Agents, Aminosteroids, Neurotoxins, antithrombotics, antioxidants, anticoagulants, antiplatelet agents, thrombolytics, antiproliferatives, anti-
5 inflammatories, antimitotic, antimicrobial, anti-restenosis, smooth muscle cell inhibitors, antibiotics, fibrinolytic, immunosuppressive, antiangiogenic, antirestenotic antineoplastic, antimigrative, antigenic agents or combinations thereof. More specifically, examples of the pharmaceutical agent include, but are not limited to, everolimus, sirolimus, pimecrolimus, tacrolimus, zotarolimus,
10 biolimus, paclitaxel, rapamycin and combination thereof.

[0020] According to one embodiment of the present disclosure, the diameter of the nanoparticle of the present invention is in the range of about 10 nm to about 950 nm, preferably about 100 nm to about 900 nm, more preferably about 200 nm to about 800 nm.

15 **[0021]** According to one embodiment of the present disclosure, the ratio of biodegradable polymer to the pharmaceutical agent is in the range of 90:10 to 10:90.

[0022] According to one embodiment of the present disclosure, the ratio of phospholipid-based molecules to the pharmaceutical agent is in the range of 90:10
20 to 10:90.

[0023] One aspect of the present disclosure is to provide a lipid-polymer hybrid nanoparticle, wherein the pharmaceutical agent is not uniformly dispersed in the polymeric core of the micelle but accumulated on its periphery. Specifically, the pharmaceutical agent molecules get concentrated in the shell
25 structure of the nanoparticles, on and in proximity to the inner periphery of the shell. Hence, the lipid-based shell and proximal inner area becomes a primary excipient part of the nanoparticle and the biodegradable polymer containing core becomes a secondary excipient part of the nanoparticle. The shell structure is made of the lipid molecules, either of one kind or a mixture of different types of
30 lipids. Only a minor amount of the pharmaceutical agent is dispersed in the main

biodegradable polymeric core. Micelles are created by mixing of organic liquid phase and aqueous phase in presence of surfactants whereas the distribution of a particular compound between these two phases can be controlled using its solubility in these two phases. On addition, the hydrophobic nature of the pharmaceutical agent and its interaction with the biodegradable polymer and the lipids, result in concentrating the pharmaceutical agent near the periphery of the nanoparticle. Further, the added surfactants, mixing speed and mixing time are other variables that may decide the extent of nanoparticle formation and size distribution of the nanoparticles.

10 **[0024]** Further, as discussed above, a careful selection of the solvents (solvent and antisolvent) and surfactants is instrumental in controlling the movement of the pharmaceutical agent and the area of accumulation of the pharmaceutical agent in nanoparticles of a drug delivery system. This movement and accumulation area in the nanoparticles decide the drug release profile of the drug delivery system.

15 **[0025]** According to another embodiment of the present disclosure, primarily organic, non-aqueous solvents are selected that have different solubilities, or of different Hansen solubility parameters, for biodegradable polymer, pharmaceutical agent and phospholipids. Further, phospholipids act as surfactants in this system and the phospholipids provide stability to nanoparticles or micelles and avoid their aggregation during preparation as well as storage to maintain their characterization as nanoparticles. Solubility difference between the solvents biases the pharmaceutical agent molecule movement towards the micelles in biodegradable polymeric matrix but the lipophilic nature of the pharmaceutical agent drives them towards the phospholipid molecules that also have an affinity
20 towards the hydrophobic pharmaceutical agent. Hence, the selected solvent-anti solvent interact with this dual affinity, and drive the majority of the pharmaceutical agent towards the periphery where the pharmaceutical agent gets concentrated near the phospholipid molecules which are forming the periphery of the micelles or nanoparticles, and a minor amount of the pharmaceutical agent
25 remains inside the micelle and distributed in the biodegradable polymeric core.
30

[0026] Further, in process of preparing the nanoparticles, the hydrophilic portion of the micelle forming surfactant is towards the outer side of the periphery of the nanoparticle. During the formation of the nanoparticle and accumulation of the pharmaceutical agent near the phospholipid molecules, the majority of the accumulated pharmaceutical agent is adhered to the phospholipids and accumulates on the inner side of the periphery of the nanoparticle that is formed by the phospholipids. In some variants, phospholipids are functionalized by hydrocarbon chain containing hydrophilic compounds e.g. PEGylated phospholipids. In such cases, the PEG chains, being hydrophilic in nature, are also situated on outer periphery of the nanoparticle. Optionally, these hydrocarbon chains may also hold the pharmaceutical agent in minor amount due to physical adhesion forces between the pharmaceutical agent molecules and the hydrocarbon chains. In addition, during nanoparticle formation process, some of the pharmaceutical agent is not entrapped inside the nanoparticles and remains in the system as free pharmaceutical agent. On solvent removal or on separating the formed nanoparticles from process medium, a fraction of the free pharmaceutical agent remains present on or in between the nanoparticles. Non-ionic phospholipids, anionic phospholipids, cationic phospholipids, zwitterionic phospholipids or a combination thereof can also be used in preparation of the nanoparticles as per the present disclosure.

[0027] On exposing such nanoparticles to biological tissues, the combined hydrophilic and lipophilic nature of phospholipids on the outer side of the periphery help in adhering the nanoparticles with the tissue boundary and easily penetrating the tissue boundary. Due to enhanced compatibility between the nanoparticle and the tissue, a good amount of the pharmaceutical agent is transferred to the tissue and retained inside the tissue. On exposure of the nanoparticles to the tissue, an initial burst of the pharmaceutical agent release takes place that lasts almost a day. This initial burst of the pharmaceutical agent results due to the pharmaceutical agent present in between the nanoparticles as free pharmaceutical agent molecules from the manufacturing process and/or due to the pharmaceutical agent loosely adhered to the outer periphery of the

nanoparticle. . The pharmaceutical agent release for next few days is slower and in a controlled manner. This release is controlled due to adhesion between the pharmaceutical agent and the phospholipid-based boundary of the nanoparticle. This controlled release continues for 5 to 7 days. Hence, from the exposure time, the first two phases together complete in 6 to 8 days from exposure time. After the controlled release, a sustained release of the pharmaceutical agent is observed over next 18 – 22 days. The sustained release profile takes place once the pharmaceutical agent containing biodegradable polymeric core is exposed to the tissue.

10 [0028] Hence, the nanoparticles as per this disclosure, enable a controlled pharmaceutical agent release and then a sustained pharmaceutical agent release. The nanoparticle boundary composition increases transfer of the pharmaceutical agent in the tissue and longer retention of the pharmaceutical agent in the tissues. This novel nanoparticle-based pharmaceutical agent delivery system of the present invention provides sustained pharmaceutical agent release with lower polymer load compared to conventional polymeric matrix-based pharmaceutical agent delivery systems. In present invention, formulated nanoparticles show a controlled release profile in initial few days and a sustained release profile later. The controlled release profile occurs due to the pharmaceutical agent encapsulated and accumulated near the inner periphery of the nanoparticles. The sustained release profile takes place due to the pharmaceutical agent dispersed in the polymeric core of the nanoparticles.

25 [0029] In an embodiment, phospholipids used in the preparation of the nanoparticles is functionalized by Polyethylene Glycol chains. This functionalized phospholipid or the PEGylated phospholipids present in the nanoparticles further enhance the tissue interaction due to the hydrophilic nature of PEG chains. Further, in other possible embodiments, another hydrophilic moiety containing compound can be used to functionalize the phospholipids. Such compounds include, but are not limited to Poly(carboxybetaine) (PCB), branched PEG, poly(sarcosine), polyglycerol, poly(hydroxyethyl-L-asparagine) (PHEA),

poly(vinylpyrrolidone) (PVP), poly(*N,N*-dimethylacrylamide) (PDMA), poly(*N*-acryloyl morpholine) (PACM), poly[*N*-(2-hydroxypropyl)] methacrylamide (HPMA), and poly(2-methyl-2-oxazoline) (PMOX), poly(2-ethyl-2-oxazoline), poly-(acrylic acid) or a combination thereof. Based on the functionality, the pharmaceutical agent release behavior of the nanoparticle, containing functionalized phospholipid, may have differing effect in different embodiments.

[0030] According to another embodiment, the nanoparticles prepared as per the present disclosure are applied on the target lesion either alone or in combination with a base material. The base material selected from at least a polymeric material, a non-polymeric material or a combination thereof. In addition, these nanoparticles can also be used with other drug delivery methods such as pills, eye drops, nasal sprays, ointments, intravenous route, intramuscular route, intranasal route, sublingual administration, transdermal, oral, intravaginal, intramucosal or through drug pumps placed in desired body organ or duct.

[0031] According to yet another embodiment, the nanoparticles prepared as per the present disclosure can be used in pure form, in a formulation form, in a composition form along with a polymeric medium or a non-polymeric medium. In addition, these nanoparticles can also be used in fluidic form, in aerosol, as a gel, as a powder, in a colloidal solution, in a curable mixture, in semi-solid form or in solid form.

[0032] According to one embodiment of the present disclosure, the nanoparticles prepared as per the present disclosure are used in a coating composition coated on a surface and the loading of the pharmaceutical agent in the coating is in the range of about 0.05 $\mu\text{g}/\text{mm}^2$ to 5.0 $\mu\text{g}/\text{mm}^2$, preferably about 0.5 $\mu\text{g}/\text{mm}^2$ to 4.0 $\mu\text{g}/\text{mm}^2$, more preferably about 1.0 $\mu\text{g}/\text{mm}^2$ to 3.0 $\mu\text{g}/\text{mm}^2$.

[0033] According to one embodiment of the present disclosure, the nanoparticles prepared as per the present disclosure are used in a coating composition coated on a surface and the loading of the biodegradable polymer in the coating is in the range of about 0.1 $\mu\text{g}/\text{mm}^2$ to 10.0 $\mu\text{g}/\text{mm}^2$, preferably about 0.5 $\mu\text{g}/\text{mm}^2$ to 7.0 $\mu\text{g}/\text{mm}^2$, more preferably about 1.0 $\mu\text{g}/\text{mm}^2$ to 5.0 $\mu\text{g}/\text{mm}^2$.

[0034] According to one embodiment of the present disclosure, the nanoparticles prepared as per the present disclosure are used in a coating composition on a surface and the amount of phospholipid-based molecules present in the coating is in the range of about 0.1 $\mu\text{g}/\text{mm}^2$ to 10.0 $\mu\text{g}/\text{mm}^2$,
5 preferably about 0.5 $\mu\text{g}/\text{mm}^2$ to 7.0 $\mu\text{g}/\text{mm}^2$, more preferably about 0.5 $\mu\text{g}/\text{mm}^2$ to 5.0 $\mu\text{g}/\text{mm}^2$.

[0035] Lipid-based shell ensures better adhesion to the biological tissues and nano-sized particles are easier to pass through the cell boundaries in the biological tissues resulting in better pharmaceutical agent transfer and lower loss of the
10 pharmaceutical agent due to washout by the blood flow. On application, a composition comprising such nanoparticles provide initially a controlled release with a slower release rate and then a sustained release at a higher release rate of the pharmaceutical agent, enhanced tissue absorption, longer tissue retention and better therapeutic efficacy at lower amount of the pharmaceutical agent. In
15 addition, due to organic nature of the drug delivery system, it is easier to coat these nanoparticles or nanoparticle-based coating compositions.

[0036] According to one embodiment, the drug delivery system of the present invention comprises a medical device which can be placed inside a lumen or a duct or a tract of a human or animal, selected from, but not limited to, artery, vein,
20 bile duct, urinary tract, alimentary tract, tracheobronchial tree, cerebral aqueduct or genitourinary system. Specifically, the medical device can be used endovascularly in renal artery, femoral artery, superficial femoral artery, popliteal artery, tibial artery, genicular artery, cerebral artery, carotid artery, vertebral artery, subclavian artery, radial artery, brachial artery, axillary artery, coronary
25 artery, peripheral artery, iliac artery or neuro-arteries.

[0037] According to yet another embodiment, the nanoparticle or a nanoparticle composition in accordance with the present invention is used as a medicament to be coated on a medical device for drug delivery, wherein the medical device is to be implanted in a lumen or a tract or a duct selected from bile
30 duct, urinary tract, alimentary tract, tracheobronchial tree, cerebral aqueduct,

genitourinary system, renal artery, femoral artery, superficial femoral artery, popliteal artery, tibial artery, genicular artery, cerebral artery, carotid artery, vertebral artery, subclavian artery, radial artery, brachial artery, axillary artery, coronary artery, peripheral artery, iliac artery, neuro-artery or any vein.

- 5 **[0038]** Another aspect of the present disclosure is to provide a method of preparing a nanoparticle by Solvent-Antisolvent method that provides controlled and increased pharmaceutical agent release over a longer period of time, reduced pharmaceutical agent loss due to blood flow, and increased pharmaceutical agent transfer and longer retention in the biological tissues after application. The
- 10 method comprises: (1) preparing a solution A of a pharmaceutical agent and a biodegradable polymer in an organic solvent; (2) preparing a solution B of at least one lipid in a mixture of an other organic solvent and water; (3) solution A slowly being added into solution B while solution B is being stirred by a magnetic stirrer to form micellar cores in nanometre range, at ambient temperature, wherein
- 15 volume of solution B is in excess of solution A and the ratio of Solution A to solution B is in the range of 1:50, preferably 1:40, and more preferably, 1:25; and (4) using the mixture containing nano-sized micellar cores or nanoparticles for application or further processing. The organic solvents used in solution A and solution B have differing solubility, or Hansen solubility parameter, for the
- 20 pharmaceutical agent and the biodegradable polymer. The organic solvent used in preparing solution A has good solubility for the pharmaceutical agent as well as the biodegradable polymer whereas the other organic solvent used in preparing solution B has good solubility for the lipids. However, for micelle formation, the pharmaceutical agent and the biodegradable polymer should not have good
- 25 solubility in the other organic solvent. In the present disclosure, the other organic solvent is carefully selected in which the pharmaceutical agent is soluble in some extent, but this solubility is significantly less than the solubility of the pharmaceutical agent in the organic solvent. Hence, on addition of solution A in solution B, under stirring, forms micelles where inside core comprises of the
- 30 solution of biodegradable polymer and the pharmaceutical agent in the organic solvent. The shell of the micelles is formed of the lipids present in solution B.

Initially, the pharmaceutical agent is uniformly dispersed in the micelles but as the process progresses, due to the solubility difference of the pharmaceutical agent between the inside core phase and the solution B phase outside the lipid boundary, a solubility gradient forms and some of the pharmaceutical agent molecules move
 5 towards the lipid boundary. Adhesion forces between the pharmaceutical agent, the biodegradable polymer and the phospholipids also play a role in the accumulation of the pharmaceutical agent near the inner periphery of the nanoparticle. Some of the pharmaceutical agent molecules present in the system also get accumulated on the outer periphery of the micelle and some of them also
 10 get entrapped in the molecular structure of the lipids present at the boundary, specifically towards the inner side. Hence, through a careful selection of the materials and process parameters, lipid polymer hybrid nanoparticles are formed, as per the present disclosure, which provide required properties on application.

[0039] According to one embodiment of the present disclosure, the solution
 15 B is prepared using a plurality of phospholipids selected from natural phospholipid, synthetic phospholipid or a combination thereof. Examples of the phospholipid include, but are not limited to, lecithin, soybean lecithin, egg yolk lecithin, a synthetic phospholipid, a pegylated phospholipid, phosphatidylcholine, phosphatidic acid, phosphatidylethanolamine, phosphatidylglycerol,
 20 phosphatidylserine, phosphatidylinositol, 1,2-Dimyristoyl-sn-glycero-3-phosphoethanolamine(DMPE), 1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamine(DPPE), 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine(DSPE), 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine(DOPE), 1,2-Dimyristoyl-rac-glycero-3-phospho-rac-(1-glycerol (DMPG), 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-rac-glycerol)(DOPG), 1,2-Distearoyl-sn-glycero-3-phospho-(1'-rac-glycerol)(DSPG), 1,2-Dimyristoyl-sn-glycero-3-phosphocholine(DMPC), 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine(DPPC), 1,2-Distearoyl-sn-glycero-3-phosphocholine(DSPC), 1,2-Dioleoyl-sn-Glycero-3-Phosphocholine(DPOC), 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine(POPC), 1,2-Dierucoyl-sn-glycero-3-phosphocholine(DEPC) or a combination thereof.
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[0040] According to one embodiment of the present disclosure, the method further comprises a step of removing the nanoparticle-rich phase from the solvent mixture using a suitable unit operation such as centrifugal separation, gravity settling, ultracentrifugation, electrophoresis, nanofiltration, chromatography, colloidal suspension and selective precipitation.

[0041] According to one embodiment of the present disclosure, the method further comprises a step of addition of a cryoprotectant to provide stability to the nanoparticles before lyophilization. The cryoprotectant can be selected from, but is not limited to, polyols, sugars, including sucrose, trehalose, lactose, mannitol or a combination thereof.

[0042] According to one embodiment of the present disclosure, the method further comprises a step of removing solvents from the nanoparticle-rich phase to obtain nanoparticles in powder form by using a suitable unit operation such as freeze-thaw drying or evaporation. At the time of application, the obtained nanoparticle powder is redispersed in a suitable solvent alone or in combination with suitable surfactants.

[0043] By combining different materials and process variations explained above, a variety of configurations can be obtained with varying structure-property relationships.

[0044] According to one embodiment of the present disclosure, a drug delivery system comprises a medical device coated with the nanoparticles or nanoparticle-based composition. The medical device may be selected from a group comprising of but not limited to, stent, guide wire, catheter, shunt, balloon, heart valve, vena cava filter, vascular graft, stent graft, bone prosthesis, spine prosthesis, hip prosthesis, rib prosthesis, skull prosthesis, sutures, staples, anastomosis device, bone pin, suture anchor, hemostatic barrier, vascular implant, tissue scaffold, bone substitute and intraluminal devices.

[0045] According to another embodiment of the present disclosure, the nanoparticles or nanoparticle-based composition or a formulation can be coated

through spray coating, dip coating, chemical vapor deposition, physical vapor deposition, Plasma enhanced chemical vapor deposition, evaporating deposition, sputtering deposition, ion plating, atmospheric pressure plasma deposition, sol-gel method and 3-D printing.

5 **[0046]** According to another embodiment of the present invention, the nanoparticles or a nanoparticle-based composition as per the present invention, is placed on a medical device made of a metal, metallic alloy, non-metal, polymer, polymer composite or a material made of combinations thereof. According to yet another embodiment of the present invention, the nanoparticles or a nanoparticle-based composition as per the present invention is utilized in a medical device
10 which may be an implantable medical device, a temporary implantable device or a non-implantable medical device.

[0047] Now, reference is made to the accompanying drawings which form a part hereof, and in which is shown by way of illustration a specific embodiment in
15 which the invention may be practiced. It is to be understood that other embodiments may be utilized, and structural changes may be made without departing from the scope of the present invention.

[0048] FIG. 1 illustrates a schematic diagram of an embodiment of a nanoparticle (100), according to the present disclosure. The nanoparticle (100) comprises a biodegradable polymer, specifically PLGA, based polymeric core (108) that also comprises a pharmaceutical agent, specifically Sirolimus, (104). The polymeric core is surrounded by a lipid-based shell structure. The lipid-based shell structure is made of lipids, preferably a mixture of natural and synthetic lipids, more specifically the lipid-based shell structure is made of phospholipids
20 (106) and PEGylated lipids (102). Majority of the pharmaceutical agent is accumulated on the inner side of the lipid shell structure and not uniformly dispersed in the biodegradable polymer based polymeric core. These nanoparticles allow controlled pharmaceutical agent release followed by sustained release with a higher rate of release, better permeation in biological tissues, longer retention in
25 the tissues and reduced wash out due to blood flow.
30

Examples:

[0049] Given below are two examples describing two compositions and process to prepare such nanoparticles which can be used in preparing coating compositions. Further, a set of graphs explain the pharmaceutical agent release

Example	Concentration (% w/v)				Solvent	Anti-solvent
	Sirolimus	PLGA	Natural phosphatidylcholine	PEGylated Synthetic Phospholipids		
1	0.08	0.22	0.05	0.05	Acetonitrile	Methanol
2	0.08	0.22	0.05	0.075	Acetonitrile	Methanol

5 profile and pharmaceutical agent transfer and retention profile of such nanoparticle containing compositions. Also, in one graph, pharmaceutical agent transfer and retention profile is compared with a competitor's product that is commercially available. The table below shows composition of main ingredients of two compositions :

10

Table 1: Compositions for Preparation of Sirolimus containing nanoparticles with PLGA as core and Natural phosphatidylcholine and PEGylated Synthetic Phospholipids as lipid shell

15 [0050] **Example 1:** Antiproliferative drug Sirolimus is used as the pharmaceutical agent enclosed in the micellar core. Referring to the process described in embodiments above for preparing a drug nanocarrier, solution A is prepared using Sirolimus and PLGA in acetonitrile. The concentration of Sirolimus in the solution is 0.08%w/v and the concentration of PLGA in the
 20 solution is 0.22%w/v. Another solution B is prepared using PEGylated Synthetic Phospholipids and Natural phosphatidylcholine in methanol. The concentration of

PEGylated Synthetic Phospholipids in the solution is 0.05 %w/v and the concentration of Natural phosphatidylcholine in the solution is 0.05 %w/v. Solution A is added into solution B at a rate of 1 ml/minute while solution B is being stirred at a speed of 500 RPM (Revolutions per minute) for one hour to form nano-sized micellar cores. The process takes place at ambient temperature and pressure.

[0051] **Example 2:** Antiproliferative drug Sirolimus is used as the pharmaceutical agent enclosed in the micellar core. Referring to the process described in embodiments above for preparing a drug nanocarrier, solution A is prepared using Sirolimus and PLGA in acetonitrile. The concentration of Sirolimus in the solution is 0.08%w/v and the concentration of PLGA in the solution is 0.22%w/v. Another solution B is prepared using PEGylated Synthetic Phospholipids and Natural phosphatidylcholine in methanol. The concentration of PEGylated Synthetic Phospholipids in the solution is 0.075 %w/v and the concentration of Natural phosphatidylcholine in the solution is 0.05 %w/v. Solution A is added into solution B at a rate of 1 ml/minute while solution B is being stirred at a speed of 500 RPM (Revolutions per minute) for one hour to form nano-sized micellar cores. The process takes place at ambient temperature and pressure.

[0052] Further, the pharmaceutical agent release from the nanoparticles prepared according to the present invention and the embodiments described above, is measured in a simulated physiological environment and results are depicted in FIG. 2. For this measurement, such nanoparticles sample of 1.5 to 2.5 mg weight were placed in 1.5 ml centrifuge vial with 1.5 ml release media (pH 7.4). The vials were incubated at 37 °C with gentle mixing at 200 rpm. The release media is removed from the vials at regular time intervals and quantity of the released pharmaceutical agent is measured by Liquid chromatograph method. For each sample, this measurement was done for a period of 28 days. FIG. 2 shows a release profile of the pharmaceutical agent over this period of 28 days. After an initial burst of the pharmaceutical agent on first or second day, a controlled

release is observed for next six or seven days. Afterwards, a sustained release is observed over next three weeks.

[0053] Further, in another experimental setup, the pharmaceutical agent transfer and retention profile (ex-vivo) was studied, and the results are depicted in FIG. 3.

5 In this study, balloon part of a typical balloon catheter is coated with the nanoparticles prepared according to the present invention and the embodiments described above. The coated balloon is navigated through a trackability path and inflated in a biological tissue. The amount of pharmaceutical agent loss during the navigation, amount of the pharmaceutical agent transfer to the biological tissue and amount of the pharmaceutical agent remaining on the balloon are measured.
10 For pharmaceutical agent retention measurements, the biological tissue containing compartment is attached to a pulsatile pump and a biological media passes thorough compartment for 1 hr. The amount of pharmaceutical agent adhered on the wall or retained in the wall of biological tissue and the amount of
15 pharmaceutical agent washed off in the biological media are measured at the end of first hour from balloon inflation in the biological tissue and at the end of 24th hour as well. FIG. 3 shows the amount of the pharmaceutical agent transferred at the time of balloon inflation in the biological tissue and then the absorption and retention of the pharmaceutical agent in the biological tissue at the end of the first
20 hour from balloon inflation in the biological tissue and at the end of the 24th hour. The graph clearly shows a sustained availability of the pharmaceutical agent in the biological tissue over a time period of 24 hours for the nanoparticles prepared according to example 1 and example 2.

[0054] In addition, in same experimental setup, the pharmaceutical agent transfer and retention profile (ex-vivo) was continuously studied for the nanoparticles prepared as per example 1 for a time period of 72 hours from balloon inflation in the biological tissue and the results are depicted in FIG. 4. In addition, similar study was conducted for a commercially available product from a competitor (for comparison or as a reference product). The graph in FIG. 4 clearly shows a
30 sustained pharmaceutical agent retention in the biological tissue over a period of

72 hours. Further, the graphs also distinguish the present invention from a comparative commercial product in terms of higher pharmaceutical agent transfer and higher pharmaceutical agent retention in the biological tissue.

[0055] FIG. 2, FIG. 3, and FIG. 4 clearly demonstrates that the nanoparticles prepared as per the embodiments of the present disclosure are prepared using a biodegradable polymer-based core and the lipid molecules form boundary or shell. Majority amount of the pharmaceutical agent is accumulated on the inner periphery of the shell structure formed by the lipid molecules at the periphery of such nanoparticles and minor amount of the pharmaceutical agent is dispersed in the main polymeric core. This distribution of the pharmaceutical agent allows controlled and sustained drug release over a period of three to four weeks. Also, significant increase in the drug transfer and in the drug retention in biological tissues is also evidenced.

[0056] The nanoparticles prepared as described in above exemplary embodiments or such nanoparticles containing composition can be used for application directly. Further, such nanoparticles can be further subjected to other process steps such as addition of additives for improving properties e.g., cryoprotectants for stability enhancement or lyophilization (freeze-thaw) to form the nanoparticles in powder form for storage and later application.

[0057] The present disclosure reduces the problem of high drug washout by the application of the novel nanoparticle composition. Furthermore, nano-sized particles and lipid-based shell surface make them adherable and permeable to biological tissues, such that it is administrable not only intravenously, but also via various routes including subcutaneously, dermally, orally, mucously, sublingually, and ocularly, to enable new application platforms for drug delivery in the future.

[0058] In the above description, for purpose of explanation, specific details are set forth in order to provide an understanding of the present disclosure. It will be apparent, however, to one skilled in the art that the present disclosure may be practiced without these details. One skilled in the art will recognize that embodiments of the present disclosure, one of which is described below, may be

incorporated into a number of systems. Further, structures and process shown in the figures are illustrative of exemplary embodiment of the present disclosure and are meant to avoid obscuring the present disclosure.

CLAIMS:

1. A nanoparticle for drug delivery comprising:
a peripheral primary excipient made of phospholipid-based molecules; an
5 inner biodegradable polymeric core being the secondary excipient wherein
at least one pharmaceutical agent is distributed across both the primary
excipient and the secondary excipient.
2. The nanoparticle for drug delivery, as claimed in claim 1, wherein the
biodegradable polymeric core comprises at least one polymer selected
10 from a group comprising lactose, glycol, glycolide, lactide, caprolactone or
combinations thereof.
3. The nanoparticle as claimed in claim 1, wherein the phospholipid-based
molecules are selected from a phospholipid, a functionalized phospholipid,
non-ionic phospholipid, anionic phospholipid, cationic phospholipid,
15 zwitterionic phospholipid or combinations thereof.
4. The nanoparticle as claimed in claim 3, wherein the phospholipid-based
molecules is an amphiphilic lipid selected from natural phospholipid,
synthetic phospholipid, lipid-polyethylene glycol conjugate, cholesterol,
PEGylated phospholipids, cationic lipids, soya phospholipids, egg
20 phospholipids, lecithin, DC-cholesterol, chemically modified cholesterol,
cholesterol conjugate or combinations thereof.
5. The nanoparticle as claimed in claim 1, wherein the size of the
nanoparticle is in the range of about 10 nm to about 950 nm.

6. The nanoparticle as claimed in claim 1, wherein the ratio of the amount of biodegradable polymer to that of pharmaceutical agent is 90:10 to 10:90.
7. The nanoparticle as claimed in claim 1, wherein the ratio of the amount of phospholipid-based molecules to that of pharmaceutical agent is 90:10 to 10:90.
8. The nanoparticle as claimed in claim 1, wherein the pharmaceutical agent is selected from antithrombotics, antioxidants, anticoagulants, antiplatelet agents, thrombolytics, antiproliferatives, anti-inflammatories, antimetabolic, antimicrobial, anti-restenosis, smooth muscle cell inhibitors, antibiotics, fibrinolytic, immunosuppressive, antiangiogenic, antirestenotic antineoplastic, antimigrative, antigenic agents, anti-cancer drug, antiproliferation drug, lipophilic drug, anti-restenosis drugs, Neurolytic agents, Quaternary ammonium salts, Sodium Channel Blockers, Anesthetics, Amino Acids, Amines, Calcium Channel Blockers, Diuretics, Vasovasoconstrictors, Neurotransmitter Chemicals, Venom, Sclerosant Agents, Anti-Nerve Growth Agents, Aminosteroids, Neurotoxins or combinations thereof.
9. The nanoparticle as claimed in claim 1, wherein the pharmaceutical agent is selected from paclitaxel, sirolimus, rapamycin, everolimus, pimecrolimus, tacrolimus, zotarolimus, biolimus, or combinations thereof.
10. The nanoparticle for drug delivery as claimed in claim 1, comprising the pharmaceutical agent in an amount such that a coating of a composition of

the said nanoparticle would comprise the pharmaceutical agent in an amount in the range of about $0.05 \mu\text{g}/\text{mm}^2$ to $5.0 \mu\text{g}/\text{mm}^2$.

11. The nanoparticle for drug delivery as claimed in claim 1, comprising the biodegradable polymer in an amount such that a coating of a composition
5 of said nanoparticle would comprise biodegradable polymer in an amount in the range of about $0.1 \mu\text{g}/\text{mm}^2$ to $10.0 \mu\text{g}/\text{mm}^2$.

12. The nanoparticle for drug delivery as claimed in claim 1, comprising the phospholipid-based molecules in an amount such that a coating of a composition of said nanoparticle would comprise the phospholipid- based
10 molecules in an amount in the range of $0.1 \mu\text{g}/\text{mm}^2$ to $10.0 \mu\text{g}/\text{mm}^2$.

13. A drug delivery system comprising a medical device coated with the nanoparticle as claimed in claim 1, wherein the medical device is selected from balloon, stent, shunt, catheter, heart valve, guidewire, vena cava
15 filter, vascular graft, stent graft, bone prosthesis, spine prosthesis, hip prosthesis, rib prosthesis, skull prosthesis, sutures, staples, anastomosis device, bone pin, suture anchor, hemostatic barrier, vascular implant, tissue scaffold, bone substitute and intraluminal device.

20 14. The nanoparticle as claimed in claim 1, for use as a medicament to be coated on a medical device for drug delivery, wherein the medical device is to be implanted in a lumen or a tract or a duct selected from bile duct, urinary tract, alimentary tract, tracheobronchial tree, cerebral aqueduct,

genitourinary system, renal artery, femoral artery, superficial femoral artery, popliteal artery, tibial artery, genicular artery, cerebral artery, carotid artery, vertebral artery, subclavian artery, radial artery, brachial artery, axillary artery, coronary artery, peripheral artery, iliac artery, neuro-artery or any vein.

15. A method for preparing the nanoparticle for drug delivery comprising:
- preparing a first solution A of a biodegradable polymer and a pharmaceutical agent in a first solvent;
 - 10 preparing a second solution B of at least one surfactant in a second solvent;
 - mixing the first solution in the second solution under continuous stirring and in excess of the second solution;
 - wherein the second solvent has higher solubility for the pharmaceutical agent in comparison to the first solvent.

16. A method for preparing nanoparticles for drug delivery as claimed in claim 13, herein the first solvent and the second solvent are selected from acetonitrile, Methyl chloride, Ethylene dichloride, Acetophenone, Ethylene carbonate, Propylene 1,2 carbonate, Methanol, Ethanol, Allyl alcohol, 1-Propanol, 2-Propanol, 1-Butanol, 2-Butanol, Isobutanol, Benzyl alcohol, Cyclohexanol, 1-Decanol, acetonitrile, Acetone, heptane, Hexane, Ethanolamine, Nitromethane and a combination thereof.

17. A method for preparing nanoparticles for drug delivery as claimed in claim 13, wherein the first solvent is acetonitrile and the second solvent is methanol.
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18. A method for preparing nanoparticles for drug delivery as claimed in claim 13, wherein the first solvent has Hansen solubility parameter value between 18-25 and the second solvent has Hansen solubility parameter value in range of 25-40.
- 10
19. A method for preparing nanoparticles for drug delivery as claimed in claim 13, wherein the first solvent has Hansen solubility parameter value between 18-25 and the second solvent has Hansen solubility parameter value in range of 10-15.
- 15
20. A method for preparing nanoparticles for drug delivery as claimed in claim 13, further comprises a step of removing the nanoparticle-rich phase from the solvent mixture.
- 20
21. A method for preparing nanoparticles for drug delivery as claimed in claim 13, further comprising a step of addition of a cryoprotectant to provide stability to the nanoparticles.

22. A method for preparing nanoparticles for drug delivery as claimed in claim 13, wherein the cryoprotectant is selected from, polyols, sugars, sucrose, trehalose, lactose, mannitol or a combination thereof.

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