US 20030148996A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0148996 A1**

Rubinfeld et al. (43) **Pub. Date: Aug. 7, 2003**

(54) **CAMPTOTHECIN COMPLEXES**

(76) Inventors: **Joseph Rubinfeld**, Danville, CA (US); **Simeon M. Wrenn JR.**, Danville, CA (US)

Correspondence Address:
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 943041050

(21) Appl. No.: **10/319,783**

(22) Filed: **Dec. 13, 2002**

Related U.S. Application Data

(63) Continuation of application No. 09/539,982, filed on Mar. 31, 2000, now abandoned.

Publication Classification

(51) **Int. Cl.**[7] **A61K 31/724**; C08B 37/16

(52) **U.S. Cl.** **514/58**; 536/46

(57) **ABSTRACT**

Disclosed are compositions that include a camptothecin and an amorphous cyclodextrin. The camptothecin may be substituted or unsubstituted. Also disclosed are methods of treating undesirable or uncontrolled cell proliferation by administering the inventive compositions. Finally, implants including an implant structure and the inventive composition are disclosed.

CAMPTOTHECIN COMPLEXES

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application is a continuation of U.S. application Ser. No. 09/539,982, filed Mar. 31, 2000, entitled "Camptotechin Complexes" and is hereby incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The present invention relates to improved formulations for the administration of certain camptothecin complexes.

[0004] 2. Description of Related Art

[0005] 20(S)-camptothecin (CPT), a plant alkaloid, was found to have anticancer activity in the late 1950's. Wall, M. et al., *Plant antitumor agents. I. The isolation and structure of camptothecin, a novel alkaloidal leukemia and tumor inhibitor from Camptotheca acuminata,* J. Am. Chem. Soc. 88: 3888-3890, (1966); Monroe E. Wall et al., *Camptothecin: Discovery to Clinic,* 803 Annals of the New York Academy of Sciences 1 (1996). These documents, and all documents (articles, patents, etc.) cited to herein, are incorporated by reference into the specification as if reproduced fully below. The chemical formula of camptothecin was determined to be $C_{20}H_{16}N_2O_4$.

[0006] CPT itself is insoluble in water. However, during the sixties and seventies the sodium salt of CPT was derived from CPT through opening of the lactone ring using a mild base. Clinical trials were then conducted using this hydrosoluble, sodium salt derivative of CPT (CPT Na+), which was administered intravenously. The studies were later abandoned because of the high toxicity and low potency of CPT Na+. Gottlieb, J. A., et al., *Preliminary pharmacological and clinical evaluation of camptothecin sodium salt* (*NSC* 100880), Cancer Chemother. Rep. 54:461-470 (1979); Muggia, F. M., et al., *Phase I clinical trials of weekly and daily treatment with camptothecin* (*NSC* 100880): *Correlation with clinical studies,* Cancer Chemother. Rep. 56:515-521 (1972); Gottlieb, J. A. et al., *Treatment of malignant melanoma with camptothecin* (*NSC* 100880), Cancer Chemother. Rep. 56:103-105 (1972); and Moertel, C. G., et al., *Phase II study of camptothecin* (*NSC* 100880) *in the treatment of advanced gastrointestinal cancer*, Cancer Chemother Rep. 56:95-101 (1972).

[0007] Despite its potential, interest in CPT as a therapeutic remained at a low ebb until the mid-1980's. By that time, drug therapies were being evaluated for treating human cancer using human cancer xenograft lines. During these evaluations, human tumors are serially heterotransplanted into immunodeficient, so-called "nude" mice, and the mice then tested for their responsiveness to a specific drug. (Giovanella, B. C., et al., *Cancer* 52(7): 1146 (1983)). The data obtained in these studies strongly support the validity of heterotransplanted human tumors into immunodeficient mammals, such as nude mice, as a predictive model for testing the effectiveness of anticancer agents.

[0008] CPT, and later some of its substituted forms, elicited differential responses in the cell cycle of nontumorigenic and tumorigenic human cells in vitro. Although it is not yet understood why CPT and some of its substituted forms are cytostatic for nontumorigenic cells and cytotoxic for tumorigenic cells, the selective toxicity of the compounds against tumorigenic cells in vitro and in vivo was an especially interesting feature of these drugs.

[0009] Investigators began to experiment with various substituted forms of CPT. Good activity was found when various substitutions were made to the CPT scaffold. For example, 9-Amino-20(S)-Camptothecin (9AC) and 10,11-Methylendioxy-20(S)-Camptothecin (10,11 MD) are capable of having high anticancer activity against human colon cancer xenografts. Giovanella, B. C., et al., *Highly effective topoisomerase-I targeted chemotherapy of human colon cancer in xenografts*, Science 246:1046-1048 (1989).

[0010] Additionally, 9-nitrocamptothecin (9NC) has shown high activity against human tumor xenograft models. 9NC has a nine position hydrogen substituted with a nitro moiety. 9NC has inhibited the growth of human tumor xenografts in immunodeficient nude mice and has induced regression of human tumors established as xenografts in nude mice with little or no appearance of any measurable toxicity. D. Chatterjee et al., *Induction of Apoptosis in Malignant and Camptothecin-resistant Human Cells,* 803 Annals of the New York Academy of Sciences 143 (1996).

[0011] Other substituted CPT compounds that have shown promise include 7-ethyl-10-hydroxy CPT, and other 7, 9, 10, 11-substituted compounds.

[0012] However, another problem arose when testing began to be done in an in vivo environment. CPT compounds contain an α-hydroxy-δ-lactone ring functionality that may hydrolyze under physiological conditions. The lactone moiety may open up easily to yield the carboxylate form, particularly in the presence of human serum albumin (HSA), where 97% of 9NC has been observed as converting to the open lactone form. Thomas G. Burke, *Chemistry of the Camptothecins in the Bloodstream: Drug Stabilization and Optimization of Activity,* 803 Annals of the New York Academy of Sciences 29 (1996). As noted above, the biological activity of the closed lactone ring form is far greater than the activity of the open lactone ring, carboxylated form. In addition, some researchers have concluded that a closed lactone ring also may play a role in enhancing passive diffusion of the CPT molecule into cancer cells. Id.

[0013] There have been some attempts to overcome the problems associated with opening of the lactone ring. For example, Published PCT Application WO 97/28165 discloses substituted derivatives of camptothecin that are acylated with linear or cyclo alkyl or epoxy moieties at the 20 position hydroxyl moiety. A stated objective of the acylation is to retain the lactone ring and the 20 position hydroxyl group intact. However, the class of molecules disclosed suffers from the problem that the pharmacokinetics of release of the active entity, 9-substituted camptothecin, are suboptimal. No teaching or suggestion is present in the WO 97/28165 Application of how to adjust the pharmacokinetics.

[0014] Inclusion in liposomes is another solution that has been proposed in the past to improve the availability of water-insoluble compounds in various dosage forms. Liposomes are small envelopes of fat-like compounds containing

an aqueous chamber or chambers within. The water insoluble compound may be dissolved in the fat-like compound comprising the envelope of the liposome. Liposomes, however, have the disadvantage of being preferentially removed from the circulation and retained in the liver and spleen. This limits their desirability. Liposomes also have a number of other disadvantages, including potential liposome instability and possible change in the size of the liposome upon storage.

[0015] There is therefore a need for compositions, methods, apparatus, and kits that combine the desirable properties of CPT and its substituted forms with the ability to maintain a closed lactone ring structure.

SUMMARY OF THE INVENTION

[0016] The invention relates to compositions comprising a camptothecin and an amorphous cyclodextrin, and to related methods, and apparatus.

DETAILED DESCRIPTION OF THE INVENTION

[0017] In an aspect, the invention relates to a composition comprising a camptothecin and an amorphous cyclodextrin. In another aspect, the invention relates to the composition wherein the camptothecin is a substituted camptothecin. In still another aspect, the invention relates to the composition wherein the substituted camptothecin comprises 9-nitrocamptothecin, 9-aminocamptothecin, 10,11-methylendioxy-20(S)-camptothecin, 7-ethyl-10-hydroxy camptothecin, or another substituted camptothecin that is substituted in at least one of the 7, 9, 10, 11, or 12 positions. In another aspect, the invention relates to the composition of claim 3, wherein the substituted camptothecin comprises 9-nitrocamptothecin, or 9-aminocamptothecin.

[0018] In a further aspect, the invention relates to the composition wherein said amorphous cyclodextrin has a degree of substitution of 2 to 7. In still another aspect, the invention relates to the composition wherein the amorphous cyclodextrin is substantially free of pyrogenic contaminants. In a further aspect, the invention relates to the composition wherein the amorphous cyclodextrin comprises hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of β-cyclodextrin, carboxyamidomethyl-β-cyclodextrin, carboxymethyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, hydroxypropyl-β-cyclodextrin or diethylamino-β-cyclodextrin. In yet another aspect, the invention relates to the composition wherein the amorphous cyclodextrin comprises hydroxypropyl β-cyclodextrin.

[0019] In an aspect, the invention relates to the composition wherein the cyclodextrin comprises hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of γ-cyclodextrin. In a further aspect, the invention relates to the composition wherein the amorphous cyclodextrin comprises a mixture of two or more of α-, β-, or γ-cyclodextrin. In still another aspect, the invention relates to sterile aqueous solutions comprising the composition in a form suitable for parenteral administration.

[0020] In an aspect, the invention relates to the composition wherein the ratio of the weight of camptothecin to the weight of cyclodextrin compound comprises a range between 1:1 and 1:2000. In a further aspect, the invention relates to the composition wherein the ratio of the weight of camptothecin to the weight of cyclodextrin compound comprises a range of about 1:5 to 1:200. In still another aspect, the invention relates to the composition wherein the ratio of the weight of camptothecin to the weight of cyclodextrin compound comprises a range of about 1:5 to 1:50.

[0021] In yet another aspect, the invention relates to the composition wherein the camptothecin is present in an amount effective to treat undesirable or uncontrolled cell proliferation. In a further aspect, the invention relates to the composition wherein the undesirable or uncontrolled cell proliferation comprises restenosis, various cancers, insults to body tissue due to surgery, diseases that produce fibrosis of tissue, repetitive motion disorders, disorders of tissues that are not highly vascularized, and proliferative responses associated with organ transplants.

[0022] In another aspect, the invention relates to the composition wherein the various cancers comprise acute myelogenous leukemia, bladder, breast, cervical, cholangiocarcinoma, chronic myelogenous leukemia, colorectal, gastric sarcoma, glioma, leukemia, lung, lymphoma, melanoma, multiple myeloma, osteosarcoma, ovarian, pancreatic, prostrate, stomach, or tumors at localized sites including inoperable tumors or in tumors where localized treatment of tumors would be beneficial, and solid tumors. In a further aspect, the invention relates to the composition wherein the various cancers comprise pancreatic or colorectal. In an additional aspect, the invention relates to the composition wherein the composition is in a lyophilized form.

[0023] In a further aspect, the invention relates to methods of treating undesirable or uncontrolled cell proliferation comprising administering the above-mentioned composition. In another aspect, the invention relates to the method wherein the camptothecin is a substituted camptothecin. In still another further aspect, the invention relates to the method wherein the substituted camptothecin comprises 9-nitrocamptothecin, 9-aminocamptothecin, 10,11-methylendioxy-20(S)-camptothecin, 7-ethyl-10-hydroxy camptothecin, or another substituted camptothecin that is substituted at least one of the 7, 9, 10, 11, or 12 positions. In yet another aspect, the invention relates to the method wherein the substituted camptothecin comprises 9-nitrocamptothecin, or 9-aminocamptothecin.

[0024] In a further aspect, the invention relates to the method wherein said amorphous cyclodextrin has a degree of substitution of 2 to 7. In still another aspect, the invention relates to the method wherein the amorphous cyclodextrin is substantially free of pyrogenic contaminants. In yet another aspect, the invention relates to the method wherein the undesirable or uncontrolled cell proliferation comprises restenosis, various cancers, insults to body tissue due to surgery, diseases that produce fibrosis of tissue, repetitive motion disorders, disorders of tissues that are not highly vascularized, and proliferative responses associated with organ transplants. In a further aspect, the invention relates to the method wherein the various cancers comprise acute myelogenous leukemia, bladder, breast, cervical, cholangiocarcinoma, chronic myelogenous leukemia, colorectal, gastric sarcoma, glioma, leukemia, lung, lymphoma, melanoma, multiple myeloma, osteosarcoma, ovarian, pancreatic, prostrate, stomach, or tumors at localized sites includ-

ing inoperable tumors or in tumors where localized treatment of tumors would be beneficial, and solid tumors. In an aspect, the invention relates to the method wherein the various cancers comprise pancreatic or colorectal.

[0025] In an aspect, the invention relates to implants comprising an implant structure and the composition. In a further aspect, the invention relates to the implant where the implant is a time-release implant. In still another aspect, the invention relates to the implant where the implant is a gel or polymer implant. In yet another aspect, the invention relates to the implant where the implant is coated and the composition is contained in the coating. In an aspect, the invention relates to the implant where the composition is contained within the implant structure. In still another aspect, the invention relates to the implant where the implant is biodegradable or is formed in situ.

[0026] In an aspect, the invention relates to a method of treatment comprising inserting an implant into a body wherein the implant is the above-mentioned implant. In another aspect, the invention relates to a stent comprising the above-mentioned composition.

[0027] By forming a complex between camptothecin and cyclodextrins, the inventors believe that camptothecin may be better solubilized in aqueous solution and the lactone ring of camptothecin may be protected from hydrolysis. In addition, such complexes of camptothecin:cyclodextrin may have reduced ulceration effects when administered to a host. The inventive compound, compositions comprising the compound, and methods, kits, and apparatus comprising the compound and/or composition will now be described in more detail.

[0028] An appropriate place to begin describing the invention is to examine putative mechanisms of action because apprehending such mechanisms helps to put the invention in its proper context. Of course, while such an explanation is helpful, the inventors do not wish to be bound by a particular mechanism of action, because complete understanding of such mechanisms is not necessary to the practice of the invention.

[0029] Camptothecin, whether substituted or unsubstituted, is believed to intervene in the mechanism of action of the nuclear enzyme topoisomerase I (topo I), arresting cells in the S phase. It is believed that CPT accomplishes this by stabilizing the covalently linked complexes of DNA-topo I (termed cleavable complexes), thus halting the progression of replication forks. This collision of the replication fork with the cleavable complexes is believed to trigger the apoptotic pathway. Z. Darzynkiewicz et al., *The Cell Cycle Effects of Camptothecin,* 803 Annals of the New York Academy of Sciences 93 (1996). DNA strand breaks are also implicated in the cytotoxic effects of CPT. F. Traganos et al., *Induction of Apoptosis by Camptothecin and Topotecan,* 803 Annals of the New York Academy of Sciences 101 (1996).

[0030] As discussed above, CPT's activity seems to be diminished for unknown reasons when the lactone ring is opened. HSA seems to be responsible for, or at least significantly exacerbates the ring opening. Therefore, stearically protecting the camptothecin molecule by complexing it with an amorphous cyclodextrin so as to prevent the catalytic effects of HSA presumably preserves the in vivo activity of the CPT. Other mechanisms also may be at work; knowledge of the exact mechanism is not required to practice this invention.

[0031] Preferable indications that may be treated using this invention include those involving undesirable or uncontrolled cell proliferation. Such indications include restenosis, various types of cancers such as primary tumors, insults to body tissue due to surgery, diseases that produce fibrosis of tissue, repetitive motion disorders, disorders of tissues that are not highly vascularized, and proliferative responses associated with organ transplants.

[0032] Specific types of restenotic lesions that can be treated using the present invention include coronary, carotid, and cerebral lesions. Specific types of cancers that can be treated using this invention include acute myelogenous leukemia, bladder, breast, cervical, cholangiocarcinoma, chronic myelogenous leukemia, colorectal, gastric sarcoma, glioma, leukemia, lung, lymphoma, melanoma, multiple myeloma, osteosarcoma, ovarian, pancreatic, prostrate, stomach, or tumors at localized sites including inoperable tumors or in tumors where localized treatment of tumors would be beneficial, and solid tumors. In a more preferable embodiment, the types of cancer include pancreatic, and/or colorectal. Treatment of cell proliferation due to insults to body tissue during surgery may be possible for a variety of surgical procedures, including joint surgery, bowel surgery, and cheloid scarring. Diseases that produce fibrotic tissue include emphysema. Repetitive motion disorders that may be treated using the present invention include carpal tunnel syndrome. An example of cell proliferative disorders that may be treated using the invention is a bone tumor.

[0033] The proliferative responses associated with organ transplantation that may be treated using this invention include those proliferative responses contributing to potential organ rejections or associated complications. Specifically, these proliferative responses may occur during transplantation of the heart, lung, liver, kidney, and other body organs or organ systems.

[0034] The inventive compositions' and/or methods may be practiced or administered by a variety of routes, and may be administered or coadministered in any conventional dosage form. Coadministration in the context of this invention is defined to mean the administration of more than one therapeutic in the course of a coordinated treatment to achieve an improved clinical outcome. Such coadministration may also be coextensive, that is, occurring during overlapping periods of time.

[0035] The inventive compounds and/or compositions may be administered or coadministered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery (for example by catheter or stent), subcutaneously, intraadiposally, intraarticularly, or intrathecally. The compounds and/or compositions according to the invention may also be administered or coadministered in slow release dosage forms.

[0036] By cyclodextrin is meant α-, β-, or γ-cyclodextrin. Cyclodextrins are described in detail in U.S. Pat. No. 4,727,064 to Pitha et al. Cyclodextrins are cyclic oligomers of glucose; these compounds form inclusion complexes with any drug whose molecule can fit into the lipophile-seeking cavities of the cyclodextrin molecule.

[0037] If the inventive composition is to be administered parenterally, especially via the intravenous route, the amor-

phous cyclodextrin is preferably substantially free of pyrogenic contaminants. Thus the preferable compositions of matter according to the invention for parenteral administration, especially by the intravenous route, will be nonpyrogenic. Nonpyrogenic preparations according to the invention, when administered to a subject, preferably do not cause a febrile (basal body temperature raising) reaction. Although some bacterial endotoxin may be present, the amount is preferably insufficient to elicit a febrile reaction. By substantially pyrogen free is meant that the cyclodextrin contains less than about 10 U.S.P. bacterial endotoxin units per gram using the method as set forth in United States Pharmacopeia 23 (United States Pharmacopeial Convention, Rockville, Md., USA). More preferably, the cyclodextrin may contain between 0.1 and 5 U.S.P. bacterial endotoxin units per mg, under conditions specified in the United States Pharmacopeia 23.

[0038] By amorphous cyclodextrin is meant non-crystalline mixtures of cyclodextrins wherein the mixture is prepared from α-, β-, or γ-cyclodextrin. Preferably, the amorphous cyclodextrin may be prepared by non-selective additions, more preferably by alkylation of the desired cyclodextrin species. Reactions may be carried out to yield mixtures containing a plurality of components thereby preventing crystallization of the cyclodextrin. Various alkylated and hydroxyalkyl-cyclodextrins may be made, and of course will vary, depending upon the starting species of cyclodextrin and the addition agent used.

[0039] Among the amorphous cyclodextrins suitable for compositions according to the invention are hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of β-cyclodextrin, carboxyamidomethyl-β-cyclodextrin, carboxymethyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, hydroxypropyl-β-cyclodextrin and diethylamino-β-cyclodextrin. In the compositions according to the invention hydroxy-β-cyclodextrin may be preferable. The substituted γ-cyclodextrins may also be suitable, including hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of γ-cyclodextrin.

[0040] The cyclodextrin of the compositions according to the invention may be α-, β-, or γ-cyclodextrin. α-cyclodextrin contains six glucopyranose units; β-cyclodextrin contains seven glucopyranose units; and γ-cyclodextrin contains eight glucopyranose units. The molecule is believed to form a truncated cone having a core opening of 4.7-5.3 Å, 6.0-6.5 Å and 7.5-8.3 Å in α-, β-, or γ-cyclodextrin respectively. The composition according to the invention may comprise a mixture of two or more of the α-, β-, or γ-cyclodextrins. More preferably, however, the composition according to the invention will comprise only one of the α-, β-, or γ-cyclodextrins.

[0041] The particular α-, β-, or γ-cyclodextrin to be used with the particular camptothecin to form the compositions according to the invention may be selected based on the known size of the camptothecin and the relative size of the cavity of the cyclodextrin compound. Generally if the camptothecin is relatively large, a cyclodextrin having a larger cavity is used to make the composition according to the invention. Furthermore, if the camptothecin is administered with an excipient it may be desirable to use a cyclodextrin compound having a larger cavity in the composition according to the invention.

[0042] The unmodified α-, β-, or γ-cyclodextrins may be somewhat less desirable in the compositions according to the invention because the unmodified forms tend to crystallize and are relatively less soluble in aqueous solutions. Most preferable for the compositions according to the invention are the α-, α-, and γ-cyclodextrins that are chemically modified or substituted. Chemical substitution at the 2, 3, and 6 hydroxyl groups of the glucopyranose units of the cyclodextrin rings yields increases in solubility of the cyclodextrin compound.

[0043] Most preferable as the cyclodextrins in the compositions according to the invention are amorphous cyclodextrin compounds. By amorphous cyclodextrin is meant non-crystalline mixtures of cyclodextrins wherein the mixture is prepared from α-, β-, or γ-cyclodextrin. Preferably, the amorphous cyclodextrin is prepared by non-selective alkylation of the desired cyclodextrin species. Suitable alkylation agents for this purpose include but are not limited to propylene oxide, glycidol, iodoacetamide, chloroacetate, and 2-diethylaminoethlychloride. Reactions may be carried out to yield mixtures containing a plurality of components thereby potentially preventing crystallization of the cyclodextrin. Various alkylated cyclodextrins may be made, and of course will vary, depending upon the starting species of cyclodextrin and the alkylating agent used. Among the amorphous cyclodextrins suitable for compositions according to the invention are hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of β-cyclodextrin, carboxyamidomethyl-β-cyclodextrin, carboxymethyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, hydroxypropyl-β-cyclodextrin and diethylamino-β-cyclodextrin. In the compositions according to the invention, hydroxypropyl-β-cyclodextrin is preferable although the α- or γ- analogs may also be suitable.

[0044] Amorphous hydroxypropyl-β-cyclodextrin may be purchased from a number of vendors including Cerestar, Inc. (Hammond, Ind., USA) under the trade name Encapsin, or from Janssen Pharmaceuticals (Beersen, Belgium). In addition, other forms of amorphous cyclodextrin having different degrees of substitution or glucose residue number are available commercially. A method for the production of hydroxypropyl-β-cyclodextrin is disclosed in Pitha et. al., U.S. Pat. No. 4,727,064.

[0045] The use of cyclodextrins and/or cyclodextrin derivatives have been disclosed in the following U.S. Pat. Nos. 4,024,223 to Noda et al.; 4,228,160 to Szejtli et al.; 4,232,009 to Hyashi et al.; 4,351,846 to Matsumoto et al.; 4,352,793 to Yamahira et al.; 4,383,992 to Lipari; 4,407,795 to Nicolau; 4,424,209 to Tuttle; 4,425,336 to Tuttle; 4,438,106 to Wagu et al.; 4,474,811 to Masuda et al.; 4,478,995 to Shinoda et al.; 4,479,944 , to Hyashi et al.; 4,479,966 to Hayashi et al.; 4,497,803 to Harada et al.; 4,499,085 to Masuda; 4,524,068 to Szejtli et al.; 4,555,504 to Jones; 4,565,807 to Uekama et al.; 4,575,548 to Ueda et al.; 4,598,070 to Ohwaki et al.; 4,603,123 to Chiesi et al.; 4,608,366 to Hasegawa et al.; 4,659,696 , to Hiari et al.; 4,623,641 to Szejtili et al.; 4,663,316 to Ninger et al.; 4,675,395 to Fukazawa et al.; 4,728,509 to Shimizu et al.; 4,728,510 to Shibani et al.; and 4,751,095 to Karl et al.

[0046] Camptothecin, when used in the context of this invention, includes both substituted and unsubstituted camptothecins, and analogs thereof. In particular, when substi-

tuted camptothecins are used, a large range of substitutions may be made to the camptothecin scaffold, while still retaining activity. In a preferable embodiment, the camptothecin scaffold is substituted at the 7, 9, 10, 11, and/or 12 positions. Such preferable substitutions may serve to provide differential activity over the unsubstituted camptothecin compound. Especially preferable are 9-nitrocamptothecin, 9-aminocamptothecin, 10,11-methylendioxy-20(S)-camptothecin, 7-ethyl-10-hydroxy camptothecin, or another substituted camptothecin that is substituted in at least one of the 7, 9, 10, 11, or 12 positions.

[0047] Native, unsubstituted, camptothecin can be obtained by purification of the natural extract, or may be obtained from the Stehlin Foundation for Cancer Research (Houston, Tex.). Substituted camptothecins can be obtained using methods known in the literature, or can be obtained from commercial suppliers. For example, 9-nitrocamptothecin may be obtained from SuperGen, Inc. (San Ramon, Calif.), and 9-aminocamptothecin may be obtained from Idec Pharmaceuticals (San Diego, Calif.). Camptothecin and various of its analogs may also be obtained from standard fine chemical supply houses, such as Sigma Chemicals.

[0048] The inventive compositions may include conventional pharmaceutical excipients, and other conventional, pharmaceutically inactive, agents. Additionally, the compositions may include more than one camptothecin and more than one cyclodextrin, and/or additional pharmaceutically active agents.

[0049] In preferable embodiments, the inventive compositions will contain the active agents, including the inventive compound, in an amount effective to treat an indication of interest. The relative amounts of camptothecin compound and cyclodextrin may vary depending upon the intended use of the complex and the effect of the cyclodextrin on the camptothecin. Preferably, the ratio of the weight of camptothecin to the weight of cyclodextrin compound will be in a range between 1:1 and 1:5000. Within this range, the circulating availability of the camptothecin will be significantly increased when the ratio of the weight of camptothecin to the weight of cyclodextrin compound is in a range between 1:1 and 1:2000. More preferably, the weight to weight ratio of camptothecin to cyclodextrin may be in a range of about 1:5 to 1:200 and even more preferably in a range of about 1:5 to 1:50.

[0050] To produce the formulations according to the invention, a pre-weighed amount of cyclodextrin compound, which is preferably substantially pyrogen free is placed in a suitable depyrogenated sterile container. Methods for depyrogenation of containers and closure components are well known to those skilled in the art and are fully described in the United States Pharmacopeia 23 (United States Pharmacopeial Convention, Rockville, Md., USA). Generally, depyrogenation is accomplished by exposing the objects to be depyrogenated to temperatures above 400° C. for a period of time sufficient to fully incinerate any organic matter. As measured in U.S.P. Bacterial Endotoxin Units, the formulation might contain no more than about 10 Bacterial Endotoxin Units per gram of amorphous cyclodextrin. By substantially pyrogen free is meant that the cyclodextrin contains less than about 10 U.S.P. bacterial endotoxin units per gram using the U.S.P. method. More preferably, the cyclodextrin will contain between 0.1 and 5 U.S.P. bacterial endotoxin units per mg, under conditions specified in the United States Pharmacopeia 23.

[0051] Sufficient sterile water for injection may be added to the amorphous cyclodextrin, which is substantially pyrogen free, until the desired concentration of cyclodextrin is in solution. To this solution a pre-weighed amount of the camptothecin may be added with agitation and with additional standing if necessary until it dissolves. Excipients, if any are desired, may be added with or subsequent to adding the camptothecin.

[0052] The solution may then be filtered through a sterile 0.2 micron filter into a sterile holding vessel and may be subsequently filled in sterile depyrogenated vials and is capped. For products that will be stored for long periods of time, a pharmaceutically acceptable preservative may be added to the solution comprising the complex of camptothecin and cyclodextrin prior to filtration, filling and capping, or alternatively, may be added sterilely after filtration.

[0053] Additional discussion concerning preparing camptothecin/cyclodextrin compositions according to the invention may be found in V. J. Stella et al., *Cyclodextrins: Their Future in Drug Formulation and Delivery*, Pharm Res, 14(5):556-567 (1997); A. M. Myles et al., *Analysis and modelling of the structures of beta-cyclodextrin complexes*, Biochim Biophys Acta, 1199(1):27-36 (1994); H. Arima et al., *Enhanced Rectal Absorption and Reduced Local Irritation of the Anti-inflammatory Drug Ethyl 4-biphenylylacetate in Rats by Complexation with Water-soluble Beta-cyclodextrin Derivatives and Formulation as Oleaginous Suppository, J Pharm Sci,* 81(11):1119-1125 (1992); J. K. Ong et al., *Influence of Hydroxypropyl Beta-cyclodextrin on the Stability of Benzylpenicillin in Chloroacetate Buffer*, J Pharm Pharmacol, 49(6):617-621 (1997); H. Matsuda et al., *Inclusion Complexation of P-hydroxybenzoic Acid Esters with 2-hydroxypropyl-beta-cyclodextrins. On Changes in Solubility and Antimicrobial Activity*, Chem Pharm Bull (Tokyo), 41(8):1448-1452 (1993); Y. Nakai et al., *Study of the interaction of clobazam with cyclodextrins in solution and in the solid state*, Chem Pharm Bull 38(3):728-732 (1990); Y. Watanabe et al., *Absorption Enhancement of Polypeptide Drugs by Cyclodextrins. I. Enhanced Rectal Absorption of Insulin From Hollow-type Suppositories Containing Insulin and Cyclodextrins in Rabbits,* Chem Pharm Bull (Tokyo), 40(11):3042-3047 (1992).

[0054] The composition of matter according to the invention may be supplied as a dry powder or as a solution. If the composition of matter is to be injected into a subject it may be rendered sterile prior to injection. Accordingly, the composition of matter according to the invention may be supplied as a sterile cake, plug or powder or as a sterile lyophilized preparation in a sterile vial suitable for the addition of a sterile diluent, or as a sterile liquid solution in a sterile container.

[0055] If the composition is to be administered parenterally, for example intravenously, the composition of matter may be rendered-sterile prior to such administration. Any of the several known means for rendering such pharmaceutical preparations sterile may be used so long as the active pharmaceutical compound is not inactivated and the complex with the amorphous cyclodextrin is not degraded. If the active pharmaceutical compound is heat stable, the composition of matter according to the invention may be heat

sterilized. If the cytotoxic compound is not heat-stable but is not photo degraded the composition may be sterilized by exposure to ultraviolet light or by ionizing radiation. Alternatively, the composition of matter if in a powder form may be gas sterilized using, for example, ethylene oxide gas. In another alternative, the composition of matter according to the invention may be filter-sterilized using a 0.2 micron filter. If the composition of matter is an aqueous liquid, it may be filled in a sterile container and supplied as a sterile liquid ready for further dilution or injection neat. Alternatively such sterile liquids may be freeze-dried or lyophilized in a sterile container and capped.

[0056] Alternatively, the components may be sterilized by any of the known methods appropriate to preserving the composition or the camptothecin or the cyclodextrin prior to mixing in water and may be mixed using sterile equipment and technique. The solution may be lyophilized in sterile containers and capped. Prior to use the lyophilized composition of matter may be reconstituted using sterile water for injection.

[0057] The container closure system used for containing the formulation according to the invention may also be treated to remove or destroy pyrogenic substances by means known in the art prior to filling and further processing. The formulation according to the invention may be supplied as a dry lyophilized powder as mentioned above or as a sterile non pyrogenic aqueous solution in a sterile container closure system such as a stoppered vial suitable for puncturing with a sterile syringe and needle.

[0058] Alternatively the composition according to the invention may be supplied as a sterile non pyrogenic aqueous solution in a sterile syringe or syringe and needle. As a sterile solution or powder it may also include a pharmaceutically acceptable preservative. The composition according to the invention may also be included in other dosage forms in addition to those appropriate for parenteral administration. Such dosage forms may be in the form of aqueous suspensions, elixirs, or syrups suitable for oral administration, or compounded as a cream or ointment in a pharmaceutically acceptable topical base allowing the inventive camptothecins to be absorbed across the skin. In addition the formulation according to the invention may be compounded in a lozenge or suppository suitable for trans mucosal absorption.

[0059] Another therapeutically interesting route of administration or coadministration is local delivery. Local delivery of inhibitory amounts of inventive compounds and/or compositions can be by a variety of techniques and structures that administer the inventive compounds and/or compositions at or near a desired site. Examples of local delivery techniques and structures are not intended to be limiting but rather as illustrative of the techniques and structures available. Examples include local delivery catheters, site specific carriers, implants, direct injection, or direct applications.

[0060] Local delivery by a catheter allows the administration of a inventive compounds and/or compositions directly to the desired site. Examples of local delivery using a balloon catheter are described in EP 383 492 A2 and U.S. Pat. No. 4,636,195 to Wolinsky. Additional examples of local, catheter-based techniques and structures are disclosed in U.S. Pat. No. 5,049,132 to Shaffer et al. and U.S. Pat No. 5,286,254 to Shapland et al.

[0061] Generally, the catheter must be placed such that the inventive compositions can be delivered at or near the desired site. Dosages delivered through the catheter can vary, according to determinations made by one of skill, but often are in amounts effective to create a cytotoxic or cytostatic effect at the desired site. Preferably, these total amounts are less than the total amounts for systemic administration of the inventive compositions, and are less than the maximum tolerated dose. The inventive compounds delivered through catheters preferably should be formulated to a viscosity that enables delivery through a small treatment catheter, and may be formulated with pharmaceutically acceptable additional ingredients (active and inactive).

[0062] Local delivery by an implant describes the placement of a matrix that contains the inventive compositions into the desired site. The implant may be deposited by surgery or other means. The implanted matrix releases the inventive compositions by diffusion, chemical reaction, solvent activators, or other equivalent mechanisms. Examples are set forth in Lange, *Science* 249:1527-1533 (September, 1990). Often the implants may be in a form that releases the inventive compositions over time; these implants are termed time-release implants. The material of construction for the implants will vary according to the nature of the implant and the specific use to which it will be put. For example, biostable implants may have a rigid or semi-rigid support structure, with inventive composition delivery taking place through a coating or a porous support structure. Other implants may be made of a liquid that stiffens after being implanted or may be made of a gel. The amounts of inventive composition present in or on the implant may be in an amount effective to treat cell proliferation generally, or a specific proliferation indication, such as the indications discussed herein.

[0063] One example of local delivery of the inventive composition by an implant is use of a biostable or bioabsorbable plug or patch or similar geometry that can deliver the inventive composition once placed in or near the desired site. An example of such implants can be found in U.S. Pat. No. 5,429,634 to Narciso, Jr.

[0064] A particular application of use of an implant according to the invention is treatment of cell proliferation in tissue that is not highly vascularized, as discussed briefly above. An example of such tissue is bone tissue. The difficulty in treating uncontrolled proliferative cell growth in bone tissue may be exemplified by the difficulties in treating bone tumors. Such tumors are typically refractory to treatment, in part because bone tissue is not highly vascularized. An implant in or near the proliferative site may potentially have localized cytotoxic or cytostatic effects with regard to the proliferative site. Therefore, in one embodiment, the invention may be used to treat bone tumors.

[0065] Another example of local delivery by an implant is the use of a stent. Stents are designed to mechanically prevent the collapse and reocclusion of the coronary arteries. Incorporating an inventive composition into the stent may deliver the inventive composition directly to or near the proliferative site. Certain aspects of local delivery by such techniques and structures are described in Kohn, *Pharmaceutical Technology* (October, 1990). Stents may be coated with the inventive composition to be delivered. Examples of such techniques and structures may be found in U.S. Pat.

Nos. 5,464,650 to Berg et al., 5,545,208 to Wolff et al., 5,649,977 to Campbell, 5,679,400 to Tuch, EP 0 716 836 to Tartaglia et al. Alternatively, the inventive composition loaded stent may be biorotable, i.e. designed to dissolve, thus releasing the inventive composition in or near the desired site, as disclosed in U.S. Pat. No. 5,527,337 to Stack et al. The present invention can be used with a wide variety of stent configurations, including, but not limited to shape memory alloy stents, expandable stents, and stents formed in situ.

[0066] Amounts of the inventive composition delivered by the stent can vary, according to determinations made by one of skill, but preferably are in amounts effective to create a cytotoxic or cytostatic effect at the desired site. Preferably, these total amounts are less than the total amounts for systemic administration of the inventive composition, and are preferably less than the maximum tolerated dose. Appropriate release times can vary, but preferably should last from about 1 hour to about 6 months, most preferably from about 1 week to about 4 weeks. Formulations including the inventive composition for delivery of the agent via the stent can vary, as determinable by one of skill, according to the particular situation, and as generally taught herein.

[0067] Another example is a delivery system in which a polymer that contains the inventive composition is injected into the target cells in liquid form. The polymer then cures to form the implant in situ. One variation of this technique and structure is described in WO 90/03768 to Donn.

[0068] Another example is the delivery of an inventive composition by polymeric endoluminal sealing. This technique and structure uses a catheter to apply a polymeric implant to the interior surface of the lumen. The inventive composition incorporated into the biodegradable polymer implant is thereby released at the desired site. One example of this technique and structure is described in WO 90/01969 to Schindler.

[0069] Another example of local delivery by an implant is by direct injection of vesicles or microparticulates into the desired site. These microparticulates may comprise substances such as proteins, lipids, carbohydrates or synthetic polymers. These microparticulates have the inventive composition incorporated throughout the microparticle or over the microparticle as a coating. Examples of delivery systems incorporating microparticulates are described in Lange, *Science,* 249:1527-1533 (September, 1990) and Mathiowitz, et al., *J. App. Poly Sci.* 26:809 (1981).

[0070] Local delivery by site specific carriers describes attaching the inventive composition to a carrier which will direct the drug to the desired site. Examples of this delivery technique and structure include the use of carriers such as a protein or non-protein ligand (a steroid receptor conjugate, for example) or a monoclonal antibody. Certain aspects of these techniques and structures are described in Lange, *Science* 249:1527-1533.

[0071] Local delivery also includes the use of topical applications. An example of a local delivery by topical application is applying the inventive composition directly to an arterial bypass graft during a surgical procedure. Other equivalent examples will no doubt occur to one of skill in the art.

[0072] The inventive compositions may be used in the form of kits. The arrangement and construction of such kits is conventionally known to one of skill in the art. Such kits may include containers for containing the inventive compositions, and/or other apparatus for administering the inventive compositions.

[0073] It will be apparent to those skilled in the art that various modifications and variations can be made in the compounds, compositions, kits, and methods of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents. Additionally, the following examples are appended for the purpose of illustrating the claimed invention, and should not be construed so as to limit the scope of the claimed invention.

EXAMPLES

Example 1

[0074] 20(S)-camptothecin is obtained from Sigma. Hydroxypropyl-β-cyclodextrin is obtained according to U.S. Sharma et al., *Pharmaceutical and Physical Properties of Paclitaxel (Taxol) Complexes with Cyclodextrins,* J. Pharm. Sci. 84:1223-30 (1995). A composition containing the 20(S)-camptothecin and the hydroxypropyl-β-cyclodextrin is formed using the procedures generally outlined in U.S. Sharma et al. The complex is then tested for stability according to the methods of U.S. Sharma et al., and for activity using the human tumor xenograph models outlined in B. C. Giovanella et al., *Protocols for the Treatment of Human Tumor Xenografts with Camptothecins,* 803 Annals of the New York Academy of Sciences 181 (1996), and Henry S. Friedman et al., *Treatment of Central Nervous System Xenografts with Camptothecins,* 803 Annals of the New York Academy of Sciences 210 (1996).

Example 2

[0075] 9-amino-camptothecin is produced from 20(S)-camptothecin, according to literature methods. Hydroxypropyl-β-cyclodextrin is obtained according to U.S. Sharma et al., *Pharmaceutical and Physical Properties of Paclitaxel (Taxol) Complexes with Cyclodextrins*, J. Pharm. Sci. 84:1223-30 (1995). A composition containing the 9-amino-camptothecin and the hydroxypropyl-β-cyclodextrin is formed using the procedures generally outlined in U.S. Sharma et al. The complex is then tested for stability according to the methods of U.S. Sharma et al., and for activity using the human tumor xenograph models outlined in B. C. Giovanella et al., *Protocols for the Treatment of Human Tumor Xenografts with Camptothecins,* 803 Annals of the New York Academy of Sciences 181 (1996), and Henry S. Friedman et al., *Treatment of Central Nervous System Xenografts with Camptothecins,* 803 Annals of the New York Academy of Sciences 210 (1996).

Example 3

[0076] 9-aminocamptothecin is produced from 20(S)camptothecin, according to literature methods. Dimethyl-β-cyclodextrin is obtained according to U.S. Sharma et al., *Pharmaceutical and Physical Properties of Paclitaxel (Taxol) Complexes with Cyclodextrins,* J. Pharm. Sci. 84:1223-30 (1995). A composition containing the 9-nitro-camptothecin and the dimethyl-β-cyclodextrin is formed

using the procedures generally outlined in U.S. Sharma et al. The complex is then tested for stability according to the methods of U.S. Sharma et al., and for activity using the human tumor xenograph models outlined in B. C. Giovanella et al., *Protocols for the Treatment of Human Tumor Xenografts with Camptothecins,* 803 Annals of the New York Academy of Sciences 181 (1996), and Henry S. Friedman et al., *Treatment of Central Nervous System Xenografts with Camptothecins,* 803 Annals of the New York Academy of Sciences 210 (1996).

Example 4

[**0077**] 9-nitrocamptothecin is produced by nitrating 20(S)camptothecin, according to literature methods. γ-cyclodextrin is obtained according to O. Bekers et al., *2',3'-Dideoxyinosine (ddI): Its Chemical Stability and Cyclodextrin Complexation in Aqueous Media,* J Pharm Biomed Anal, 11(6):489-493 (June 1993); O. Bekers et al., *Effect of Cyclodextrins on the Chemical Stability of Mitomycins in Alkaline Solution,* J Pharm Biomed Anal, 9(10-12):1055-1060 (1991); O. Bekers et al., *Inclusion complexation of doxorubicin and daunorubicin with cyclodextrins,* J Pharm Biomed Anal, 8(8-12):671-674 (1990). A composition of 9-nitrocamptothecin and γ-cyclodextrin is formed using the procedures generally outlined in the O. Bekers et al. articles.

[**0078**] The complex is then tested for stability according to the methods generally outlined in the O. Bekers et al. articles, and for activity using the human tumor xenograph models outlined in B. C. Giovanella et al., *Protocols for the Treatment of Human Tumor Xenografts with Camptothecins,* 803 Annals of the New York Academy of Sciences 181 (1996), and Henry S. Friedman et al., *Treatment of Central Nervous System Xenografts with Camptothecins,* 803 Annals of the New York Academy of Sciences 210 (1996).

Example **5**

[**0079**] Irinotecan (Camptothecin-11) is obtained according to Nagahiro Saijo, *Clinical Trials of Irinotecan Hydrochloride (CPT, Campto Injection, Topotecin Injection) in Japan,* 803 Annals of the New York Academy of Sciences 292 (1996). 3-hydroxypropyl-cyclodextrin is obtained according to A. Yoshida et al., *Some pharmaceutical properties of 3-hydroxypropyl-and 2,3-dihydroxypropyl-beta-cyclodextrins and their solubilizing and stabilizing abilities,* Chem Pharm Bull (Tokyo), 37(4):1059-1063 (1989). A composition of irinotecan and 3-hydroxypropyl-cyclodextrin is formed using the procedures generally outlined in the A. Yoshida et al. article.

[**0080**] The complex is then tested for stability according to the methods generally outlined in the A. Yoshida et al. article, and for activity using the human tumor xenograph models outlined in B. C. Giovanella et al., *Protocols for the Treatment of Human Tumor Xenografts with Camptothecins,* 803 Annals of the New York Academy of Sciences 181 (1996), and Henry S. Friedman et al., *Treatment of Central Nervous System Xenografts with Camptothecins,* 803 Annals of the New York Academy of Sciences 210 (1996).

Example 6

[**0081**] Topotecan is obtained from Sigma. 2,3-dihydroxypropyl-β-cyclodextrin is obtained according to A. Yoshida et al., *Some Pharmaceutical Properties of 3-Hydroxypropyl-and 2,3-Dihydroxypropyl-Beta-Cyclodextrins and Their Solubilizing and Stabilizing Abilities,* Chem Pharm Bull (Tokyo), 37(4):1059-1063 (1989). A composition of topotecan and 2,3-dihydroxypropyl-β-cyclodextrin is formed using the procedures generally outlined in the A. Yoshida et al. article.

[**0082**] The complex is then tested for stability according to the methods generally outlined in the A. Yoshida et al. article, and for activity using the human tumor xenograph models outlined in B. C. Giovanella et al., *Protocols for the Treatment of Human Tumor Xenografts with Camptothecins,* 803 Annals of the New York Academy of Sciences 181 (1996), and Henry S. Friedman et al., *Treatment of Central Nervous System Xenografts with Camptothecins,* 803 Annals of the New York Academy of Sciences 210 (1996).

Example 7

[**0083**] 9-nitrocamptothecin is produced by nitrating 20(S)camptothecin, according to literature methods. A series of substituted beta-cyclodextrins are prepared, according to F. Hirayama, *Development and Pharmaceutical Evaluation of Hydrophobic Cyclodextrin Derivatives as Modified-Release Drug Carriers,* Yakugaku Zasshi, 113(6):425-437 (1993). Compositions including these beta-cyclodextrins and 9-nitrocamptothecin are formed using the procedures generally outlined in the Hirayama article.

[**0084**] These complexes are then tested for stability according to the methods generally outlined in the Hirayama article, and for activity using the human tumor xenograph models outlined in B. C. Giovanella et al., *Protocols for the Treatment of Human Tumor Xenografts with Camptothecins,* 803 Annals of the New York Academy of Sciences 181 (1996), and Henry S. Friedman et al., *Treatment of Central Nervous System Xenografts with Camptothecins,* 803 Annals of the New York Academy of Sciences 210 (1996).

Example 8

[**0085**] 20(S)-camptothecin is obtained from Sigma. A series of substituted beta-cyclodextrins are prepared, according to F. Hirayama, *Development and Pharmaceutical Evaluation of Hydrophobic Cyclodextrin Derivatives as Modified-Release Drug Carriers,* Yakugaku Zasshi, 113(6):425-437 (1993). Compositions including these beta-cyclodextrins and 20(S)-camptothecin are formed using the procedures generally outlined in the Hirayama article.

[**0086**] These complexes are then tested for stability according to the methods generally outlined in the Hirayama article, and for activity using the human tumor xenograph models outlined in B. C. Giovanella et al., *Protocols for the Treatment of Human Tumor Xenografts with Camptothecins,* 803 Annals of the New York Academy of Sciences 181 (1996), and Henry S. Friedman et al., *Treatment of Central Nervous System Xenografts with Camptothecins,* 803 Annals of the New York Academy of Sciences 210 (1996).

Example 9

[**0087**] The complex obtained in Example 1 is prepared in a gelatin capsule oral dosage formulation. The composition is administered to a patient suffering from pancreatic adenocarcinoma, according to the protocol set forth in Ethan A. Natelson et al., *Phase I Clinical and Pharmacological*

Studies of 20-(*S*)-*Camptothecin and* 20-(*S*)-9-*Nitrocamptothecin and Anticancer Agents,* 803 Annals of the New York Academy of Sciences 224 (1996). The amount of the composition administered is normalized to provide equivalent levels of 9-nitrocamptothecin to those set forth in the Natelson et al, article. The patient's condition is then monitored clinically for disease progression.

Example 10

[**0088**] Compositions of 9-nitrocamptothecin and various cyclodextrins are prepared according to Example 8. Differing release rates are determined for 9-nitrocamptothecin based upon differing cyclodextrin structures using the methods generally set forth in F. Hirayama, *Development and Pharmaceutical Evaluation of Hydrophobic Cyclodextrin Derivatives as Modified-Release Drug Carriers*, Yakugaku Zasshi, 113(6):425-437 (1993). Several different compositions having differing release times are obtained. These compositions are then individually compounded into tablets, and are administered orally to human volunteers. Blood samples are taken from the volunteers, and the amount of closed lactone and open lactone forms of the 9-nitrocamptothecin, together with release time, is determined.

Example 11

[**0089**] The composition of Example 1 is prepared. This composition is then used to prepare a coated stent, using the general teachings of Berg et al. (U.S. Pat. Nos. 5,464,650). A stenotic lesion is then induced in a conventional animal model, namely a pig artery. The nature and dimensions of the stenotic lesion are then determined using a catheter and an appropriate viewing device. The stent is then deployed at the lesion site, using a conventional stent deployment catheter and balloon. After one week, the pig is sacrificed, and the degree of restenotic growth is determined. This amount of growth is compared against a control animal where the deployed stent is not coated.

What is claimed is:

1. A composition comprising a camptothecin and an amorphous cyclodextrin.

2. The composition of claim 1, wherein the camptothecin is a substituted camptothecin.

3. The composition of claim 2, wherein the substituted camptothecin comprises 9-nitrocamptothecin, 9-aminocamptothecin, 10,11-methylendioxy-20(S)-camptothecin, 7-ethyl-10-hydroxy camptothecin, or another substituted camptothecin that is substituted in at least one of the 7, 9, 10, 11, or 12 positions.

4. The composition of claim 3, wherein the substituted camptothecin comprises 9-nitrocamptothecin, or 9-aminocamptothecin.

5. The composition of claim 1 wherein said amorphous cyclodextrin has a degree of substitution of 2 to 7.

6. The composition of claim 1, wherein the amorphous cyclodextrin is substantially free of pyrogenic contaminants.

7. The composition of claim 1, wherein the amorphous cyclodextrin comprises hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of β-cyclodextrin, carboxyamidomethyl-β-cyclodextrin, carboxymethyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, hydroxypropyl-β-cyclodextrin or diethylamino-β-cyclodextrin.

8. The composition of claim 7, wherein the amorphous cyclodextrin comprises hydroxypropyl β-cyclodextrin.

9. The composition of claim 1, wherein the amorphous cyclodextrin comprises hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of γ-cyclodextrin.

10. The composition of claim 1, wherein the amorphous cyclodextrin comprises a mixture of two or more of α-, β-, or γ-cyclodextrin.

11. A sterile aqueous solution comprising the composition of claim 1 in a form suitable for parenteral administration.

12. The composition of claim 1, wherein the ratio of the weight of camptothecin to the weight of cyclodextrin compound comprises a range between 1:1 and 1:2000.

13. The composition of claim 12, wherein the ratio of the weight of camptothecin to the weight of cyclodextrin compound comprises a range of about 1:5 to 1:200

14. The composition of claim 13, wherein the ratio of the weight of camptothecin to the weight of cyclodextrin compound comprises a range of about 1:5 to 1:50.

15. The composition of claim 1, wherein the camptothecin is present in an amount effective to treat undesirable or uncontrolled cell proliferation.

16. The composition of claim 15, wherein the undesirable or uncontrolled cell proliferation comprises restenosis, various cancers, insults to body tissue due to surgery, diseases that produce fibrosis of tissue, repetitive motion disorders, disorders of tissues that are not highly vascularized, and proliferative responses associated with organ transplants.

17. The composition of claim 16, wherein the various cancers comprise acute myelogenous leukemia, bladder, breast, cervical, cholangiocarcinoma, chronic myelogenous leukemia, colorectal, gastric sarcoma, glioma, leukemia, lung, lymphoma, melanoma, multiple myeloma, osteosarcoma, ovarian, pancreatic, prostrate, stomach, or tumors at localized sites including inoperable tumors or in tumors where localized treatment of tumors would be beneficial, and solid tumors.

18. The composition of claim 17, wherein the various cancers comprise pancreatic or colorectal.

19. The composition of claim 1, wherein the composition is in a lyophilized form.

20. A method of treating undesirable or uncontrolled cell proliferation comprising administering the composition of claim 1.

21. The method of claim 20, wherein the camptothecin is a substituted camptothecin.

22. The method of claim 21, wherein the substituted camptothecin comprises 9-nitrocamptothecin, 9-aminocamptothecin, 10,11-methylendioxy-20(S)-camptothecin, 7-ethyl-10-hydroxy camptothecin, or another substituted camptothecin that is substituted in at least one of the 7, 9, 10, 11, or 12 positions.

23. The method of claim 22, wherein the substituted camptothecin comprises 9-nitrocamptothecin, or 9-aminocamptothecin.

24. The method of claim 20, wherein said amorphous cyclodextrin has a degree of substitution of 2 to 7.

25. The method of claim 20, wherein the amorphous cyclodextrin is substantially free of pyrogenic contaminants.

26. The method of claim 20, wherein the undesirable or uncontrolled cell proliferation comprises restenosis, various cancers, insults to body tissue due to surgery, diseases that produce fibrosis of tissue, repetitive motion disorders, dis-

orders of tissues that are not highly vascularized, and proliferative responses associated with organ transplants.

27. The method of claim 26, wherein the various cancers comprise acute myelogenous leukemia, bladder, breast, cervical, cholangiocarcinoma, chronic myelogenous leukemia, colorectal, gastric sarcoma, glioma, leukemia, lung, lymphoma, melanoma, multiple myeloma, osteosarcoma, ovarian, pancreatic, prostrate, stomach, or tumors at localized sites including inoperable tumors or in tumors where localized treatment of tumors would be beneficial, and solid tumors.

28. The method of claim 26, wherein the various cancers comprise pancreatic or colorectal.

29. An implant comprising an implant structure and the composition of claim 1.

30. The implant of claim 29, where the implant is a time-release implant.

31. The implant of claim 29, where the implant is a gel or polymer implant.

32. The implant of claim 29, where the implant is coated and the composition is contained in the coating.

33. The implant of claim 29, where the composition is contained within the implant structure.

34. The implant of claim 29, where the implant is biodegradable or is formed in situ.

35. A method of treatment comprising inserting an implant into a body wherein the implant is the implant of claim 29.

36. A stent comprising the composition of claim 1.

37. The stent of claim 36, where the stent is coated and the composition is contained in the coating.

38. The stent of claim 36, where the composition is contained within the stent structure.

39. The stent of claim 36, wherein the composition is present in an amount effective to reduce undesirable or uncontrolled cell proliferation once the stent is deployed.

40. A method of treatment comprising inserting a stent into a body, wherein the stent comprises the composition of claim 1.

41. A method of treatment comprising administering the composition of claim 1 through an intraluminal catheter.

42. A method of treatment comprising administering the composition of claim 1 in a local fashion.

* * * * *