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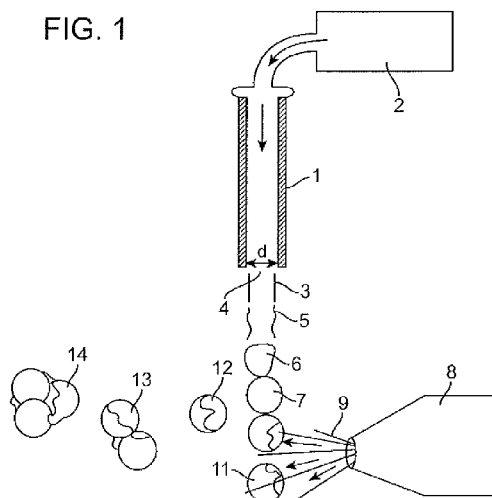
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(54) Title: CONTROLLED RELEASE VAGINAL GEL WITH ANTIVIRAL PARTICLES

FIG. 1



(57) Abstract: Formulations are disclosed which are comprised of tenofovir particles, and a biocompatible gel having the particles dispersed therein. The gel may be comprised of a flavoring agent and one or more compounds which generate heat. The particles may be provided in a plurality of groups (2, 3 or more) of different size spheres. The spheres may be comprised of tenofovir alone or in combination with emtricitabine and a controlled release polymer such as poly lactic glycolic acid (PLGA) or other suitable, biocompatible material.



CONTROLLED RELEASE VAGINAL GEL WITH ANTIVIRAL PARTICLES

FIELD OF THE INVENTION

[0001] The invention relates to a vaginal gel packaged with a formulation of controlled release tenofovir particles. More particularly the invention relates to vaginal gel formulations which improve patient compliance of tenofovir in order to inhibit HIV infection.

BACKGROUND OF THE INVENTION

[0002] Human immunodeficiency virus infection / acquired immunodeficiency syndrome (HIV/AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). During the initial infection a person may experience a brief period of influenza-like illness. This is typically followed by a prolonged period without symptoms. As the illness progresses it interferes more and more with the immune system, making the person much more likely to get infections, including opportunistic infections, and tumors that do not usually affect people who have working immune systems.

[0003] HIV is transmitted primarily via unprotected sexual intercourse, (including anal and even oral sex), contaminated blood transfusions, hypodermic needles, and from mother to child during pregnancy, delivery, or breastfeeding. Some bodily fluids, such as saliva and tears, do not transmit HIV. Prevention of HIV infection, primarily through safe sex and needle-exchange programs, is a key strategy to control the spread of the disease.

[0004] There is no cure or vaccine; however, antiretroviral treatment can slow the course of the disease and may lead to a near-normal life expectancy. While antiretroviral treatment reduces the risk of death and complications from the disease, these medications are expensive and may be associated with side effects.

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[0005] Genetic research indicates that HIV originated in west-central Africa during the early twentieth century. AIDS was first recognized by the Centers for Disease Control and Prevention (CDC) in 1981 and its cause—HIV infection—was identified in the early part of the decade. Since its discovery, AIDS has caused nearly 30 million deaths (as of 2009). As of 2010, approximately 34 million people have contracted HIV globally. AIDS is considered a pandemic—a disease outbreak which is present over a large area and is actively spreading.

[0006] HIV/AIDS has had a great impact on society, both as an illness and as a source of discrimination. The disease also has significant economic impacts. There are many misconceptions about HIV/AIDS such as the belief that it can be transmitted by casual non-sexual contact. The disease has also become subject to many controversies involving religion.

[0007] There is currently no cure or effective HIV vaccine. Treatment consists of high active antiretroviral therapy (HAART) which slows progression of the disease and as of 2010 more than 6.6 million people were taking them in low and middle income countries. Treatment also includes preventative and active treatment of opportunistic infections.

[0008] Current HAART options are combinations (or "cocktails") consisting of at least three medications belonging to at least two types, or "classes," of antiretroviral agents. Initially treatment is typically a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside analogue reverse transcriptase inhibitors (NRTIs). Typical NRTIs include: zidovudine (AZT) or tenofovir (TDF) and lamivudine (3TC) or emtricitabine (FTC). Combinations of agents which include a protease inhibitor (PI) are used if the above regime loses effectiveness.

[0009] When to start antiretroviral therapy is subject to debate. Both the World Health Organization, European guidelines and the United States recommends antiretrovirals in all adolescents, adults and pregnant women with a CD4 count less than 350/uL or those with symptoms regardless of CD4 count. This is supported by the fact that beginning treatment at this level reduces the risk of death. The United States in addition recommends them for all HIV-infected people regardless of CD4 count or symptoms,

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however makes this recommendation with less confidence for those with higher counts. While the WHO also recommends treatment in those who are co-infected with tuberculosis and those with chronic active hepatitis B. Once treatment is begun it is recommended that it is continued without breaks or "holidays". Many people are diagnosed only after the moment treatment ideally should have begun. The desired outcome of treatment is a long term plasma HIV-RNA count below 50 copies/mL. Levels to determine if treatment is effective are initially recommended after four weeks and once levels fall below 50 copies/mL checks every three to six months are typically adequate. Inadequate control is deemed to be greater than 400 copies/mL. Based on these criteria treatment is effective in more than 95% of people during the first year.

[0010] Benefits of treatment include a decreased risk of progression to AIDS and a decreased risk of death. In the developing world treatment also improves physical and mental health. With treatment there is a 70% reduced risk of acquiring tuberculosis. Additional benefits include a decreased risk of transmission of the disease to sexual partners and a decrease in mother-to-child transmission. The effectiveness of treatment depends to a large part on compliance. Reasons for non-adherence include: poor access to medical care, inadequate social supports, mental illness and drug abuse. As well the complexity of treatment regimens (due to pill numbers and dosing frequency) and adverse effects may create intentional non-adherence. Adherence is however just as good in low income as high income countries.

[0011] Specific adverse events are related to the agent taken. Some relatively common ones include: lipodystrophy syndrome, dyslipidemia, and diabetes mellitus especially with protease inhibitors.[9] Other common symptoms include: diarrhea, and an increased risk of cardiovascular disease. Adverse effects are however less with some of the newer recommended treatments. Cost may be an issue with some medications being expensive however as of 2010, 47% of those who needed them were taking them in low and middle income countries. Certain medications may be associated with birth defects and thus not suitable for women hoping to have children.

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[0012] Treatment recommendations for children are slightly different from those for adults. In the developing world, as of 2010, 23% of children who were in need of treatment had access. Both the World Health Organization and the United States recommend treatment for all children less than twelve months of age. The United States recommends in those between one year and five years of age treatment in those with HIV RNA counts of greater than 100,000 copies/mL, and in those more than five years treatments when CD4 counts are less than 500/ul.

SUMMARY OF THE INVENTION

[0013] Formulations are disclosed which are comprised of drug containing particles, and a biocompatible gel having the particles dispersed therein. The drug is a reverse transcriptase inhibitor. The gel may be comprised of a flavoring agent and one or more compounds which generate heat. The particles may be provided in a plurality of groups (2, 3 or more) of different size spheres. The spheres may be comprised of a reverse transcriptase inhibitor such as tenofovir alone or in combination with other inhibitors such as emtricitabine or lamivudine and a controlled release polymer such as poly lactic glycolic acid (PLGA) or other suitable, biocompatible material.

[0014] Formulations of the invention are designed to improve patient compliance and thereby inhibit HIV infection in at least three ways. First, the vaginal gel formulation is flavored. Second, the formulation includes one or more compounds which generate heat via an exothermic reaction. Third, the controlled release characteristics keep the active compound in place over a longer period of time.

[0015] The formulation may be comprised of groups of different sizes particles packaged separately for possible later combination with an aqueous gel comprising a flavoring agent and a compound that generates heat. Each group of spherical particles may consist of multiple particles which are all substantially the same size which together with other groups are designed to provide a combination of different drug release rates when the formulation is deployed or implanted and provide a relatively constant level of drug to the surrounding area.

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[0016] An aspect of the invention is a formulation comprised of several groups of particles wherein each group of particles is different from the particles of other groups but identical to particles within the same group. The groups of particles (which may be only two groups or three or more groups) are designed to release drug at different points in time and/or rates over time and thereby provide for therapeutic levels of drug over a period of time of 24 hours to 7 days, 1 to 2 days, 1 to 3 days, 1 to 4 days, etc. Although such groups of particles is an important aspect of the invention there must be a convenient way for the particles to be placed in the vaginal cavity where the drug is released and provides the desired therapeutic level which is a level which is sufficient to prevent HIV infection. Those skilled in the art will understand that there are different types of devices which could be used for vaginal delivery.

[0017] First, the formulation of groups of particles would be stored separately from a gel in a plunger syringe type device. Upon use the plunger mixes the particles into the gel and the mixture of particles and gel are injected into the vaginal cavity.

[0018] Second, the formulation of particles is placed in a capsule comprised of a biocompatible, dissolvable material which can be polymeric, gelatin or any biocompatible material which dissolves in vaginal fluid. The capsule could include a second capsule contained therein as well as additional capsules and the capsules designed to dissolve at different points in time thereby providing for controlled release of the drugs from the capsules.

[0019] Third, a capsule as described as above can be included within a tubular applicator of the type used in connection with the insertion of tampons. Such an applicator could also be used in connection with a gel and particle formulation stored separately within the application.

[0020] Fourth, the formulation of particles can be mixed into a gel and applied to a condom or onto a cervical cap or dome comprised of latex or silicone (e.g. a diaphragm) which is then inserted into the vaginal cavity to provide birth control along with HIV infection control.

[0021] In one embodiment the release rate of one group of particles is decreasing (or the drug released from the group is being metabolized out of the system) while the

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release rate of another group of particles is increasing (or drug from one group is being added to the system) so that the combined groups of particles making up the formulation provide a substantially constant level of drug over a therapeutically effective period of time (1-7 days). The concentrations of drug and the release rate of these drugs may be varied.

[0022] Formulations of particles may be divided into separate disposable packets which may be a single use syringe wherein each syringe of formulation includes a plurality of groups of spheres wherein the spheres of each group of spheres are all of substantially the same size. Thus, the packet may include 2, 3, 4 or more groups of spheres with a typical formulation being comprised of three groups of spheres in a small, medium, and large size. The packet of formulations is specifically designed so as to obtain a desired therapeutic effect. The desired therapeutic effect of the particles is to provide a therapeutic level of drug to an area to prevent HIV infection. If the level of the drug drops too low then the antiviral effect is lost. However, if the level is raised too high the drug becomes toxic to surrounding tissue. Still further, if the therapeutic level of the drug is not maintained for a sufficiently long period of time infection can occur. If the therapeutic level of the drug is maintained for too long of a period of time there may also be undesirable results. Thus, it is important to adjust the formulation so that the concentration of the drug delivered to the target area is not too low or too high and so that the drug is delivered for a sufficiently long period of time but not a period which is too long.

[0023] The formulation can be produced using one or more reverse transcriptase inhibitors and it can be readily prepared using known FDA approved drugs. Although the spheres within the formulation can be produced using a wide range of different polymers, the formulation is typically produced using a biocompatible widely used and accepted polymer such a polylacticglycolic acid (PLGA).

[0024] The methodology described here substantially reduces the trial and error of producing a controlled release formulation. This is done by using particles of a known size (volume and surface areas $\pm 10\%$) shape (spherical) and dissolution rate within an environment to which the particles are delivered. Because all the particles of any given

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group have substantially the same surface area from one particle to another the dissolution rate of a given particle and the group of particles can be calculated mathematically based on a known dissolution rate of a particle of known surface area. Particles in the formulation preferably have a spherical shape and a diameter in a range of from about 2 microns to about 40 microns about 10 microns ± 1 micron. The particle types may include particles comprised of drug alone, drug and polymer mixed and/or drug coated with polymer.

[0025] A typical formulation can be comprised of two groups of particles wherein the first group is comprised of particles having a diameter of about 6 microns and the second group comprised of particles having a diameter of about 20 microns. These particles have spherical conformations and each particle within each group has approximately the same size and shape with a differential $\pm 10\%$. Although the particles may be configured in different ways such as having a reverse transcriptase drug on the inside and coated polymer on the outside, a typical formulation also includes spheres where the drug and polymer are intermixed. Such spheres are easily produced by mixing the drug in the polymer and thereafter forming the spheres. Spheres can be produced using a technology such as that described within U.S. Patent 6,241,159 issued June 5, 2005 and U.S. Patent 6,174,469 issued January 16, 2001 as well as related issued U.S. and non-U.S. patents to Alfonso Ganan-Calvo all of which are incorporated herein by reference in their entirety to disclose and describe methods of making uniform sized small particles.

[0026] An aspect of this invention is to show that in addition to relying on the chemical properties of injected microparticles for their controlled release characteristics, the physical size of these particles can be used to provide another layer of control over the release profile because that the physical size of particles in different groups of particles can be controlled precisely as can the total surface area of all the particles in the group combined. When the particles are very small in size (e.g. 1-40 micrometers) the surface area differential from one group to the next can be made quite large by small changes in diameter.

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- [0027] Poly (lactide-co-glycolide) polymers (PLGA) can be used as an excipient in the creation of precisely sized microparticles for attachment to a device such as a surgical screw to produce a sustained release profile by using short chain PLGA polymer allowing the PLGA to be manipulated during the formulation process without the use of organic solvents.
- [0028] Other polymer excipients can be used if they are pharmaceutically acceptable and biocompatible with the surrounding tissue. Another useful polymer is PDLA which is poly-dl-lactic acid which has a higher glass transition point (about 45° - 55°C) than PLGA having a glass transition point of about 30° - 40°C.
- [0029] Unlike an approach which might rely solely on the chemical composition of microparticles as a means for creating controlled release formulations, the present invention relies additionally on precise sizing of the microparticles and the use of at least two different sizes of microparticles in the formulation. By exploiting the precise differences in surface area to volume ratio in the different populations of microparticles in the formulation, there is intrinsically less reliance on the chemistry of the particles to produce a sustained levels of the drug in the surrounding area. By relaxing the requirement that the chemistry will have the predominant effect on the controlled release behavior a simpler chemistry can be employed which is easier and less costly to manufacture, and which avoids the use of organic solvents during its production period. For example, short chain PLGA polymer can be employed which can be processed without the use of organic solvents.
- [0030] Poly (lactide-co-glycolides) (PLGA) compositions are commercially available from Boehringer Ingelheim (Germany) under the Resomer mark e.g. PLGA 50:50 (Resomer RG-502), PLGA 75:25 (Resomer RG-752) and d, l-PLA (Resomer RG-206) and from Birmingham Polymers (Birmingham, Alabama). These copolymers are available in a wide range of molecular weights and ratios of lactic acid to glycolic acid.
- [0031] An aspect of the invention is a biocompatible gel incorporating spherical particles which provide a desired drug release profile by combining a plurality of different groups of particles wherein each group consists of particles all of which have

a known size, number and shape so that the combined groups provide a rate of dissolution in a known environment where the gel is placed.

[0032] Another aspect of the invention is that it be comprised of a plurality (2 or more) of different groups of particles wherein the particles within each group are substantially the same in size and shape ($\pm 10\%$) and are different from one group to another group as regards the drug release profile of the particles in a particular group. The particles preferably have a size in a range of from about 1 to about 100 micrometers in diameter and more preferably about 2 to 70 or 2 to 40 or 4 to 30 micrometers in diameter.

[0033] In addition to producing formulations comprised of different groups of particles the formulation of particles is being sealed in sterile disposable containers with a gel which may include a flavoring agent and/or a heat generating compound, all of which are generally added at the point of administration. The formulation of particles may be themselves considered devices because they are comprised of polymer and drug.

[0034] An aspect of the invention is a packet of formulation comprised of a first group and a second group of particles. The particles are preferably spherical and are comprised of a biocompatible polymer and a pharmaceutically active drug which is a reverse transcriptase. The particles are generally present in an amount of about 100 or more particles wherein all of the particles within the group have substantially the same size with a margin of error $\pm 10\%$. There may be a plurality of groups of particles wherein the particles within the one group are the same with respect to each other but are different with respect to particles within another group. Further, the particle within one group have a rate of dissolution which is different from the particles within other groups thereby making it possible to provide a controlled release of the drug into the surrounding environment.

[0035] Another aspect of the invention is a formulation comprised of a plurality of particles which particles are comprised of two or more reverse transcriptase drugs and a biocompatible polymer. The particles are dispersed in a pharmaceutically acceptable carrier which may be a biocompatible gel or absorbable collagen sponge. The particles may have uniform size and shape or may be designed so as to have irregular sizes and shapes. The formulation is designed such that when it is placed on tissue such as in a

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vagina, the formulation provides a therapeutically effective dose of the drug over a period of time of greater than 1 day and less than 7 days.

[0036] In another aspect of the invention groups of particles are contained within a capsule which capsule is vaginally inserted. After insertion the capsule is dissolved and thereafter the particles within the capsule dissolve at different rates. In another embodiment the capsule is sufficiently large so as to incorporate additional capsules each of which include groups of particles wherein the different capsules dissolve at different rates so as to provide controlled sustained release of the pharmaceutically active drug locally in the vaginal cavity. The capsule is comprised of a biocompatible polymeric material which dissolves at body temperature in the presence of vaginal fluids. The capsule may include from about 100 mg to about 600 mg of pharmaceutically active drug dispersed in the particles with a pharmaceutically acceptable excipient and the pharmaceutically acceptable excipient material.

[0037] Another aspect of the invention is a formulation comprised of a biocompatible polymer and a plurality of groups of particles. The particles are comprised of a biocompatible polymer and a reverse transcriptase.

[0038] Still yet another aspect of the invention is groups of particles of biocompatible polymer with reverse transcriptase therein dispersed in a biocompatible gel such as FlosealTM which gel may be further comprised of a forming agent and/or a heat generating compound.

[0039] Another aspect of the invention is a method comprising providing particles which may be in first and second groups of particles as defined here on a sponge having therein drug on and throughout the sponge and inserting the sponge into a vagina.

[0040] 1. An aspect of the formulation, comprising:

[0041] a plurality of particles comprised of a reverse transcriptase inhibitor and a biocompatible polymer; and

[0042] a pharmaceutically acceptable gel carrier having the particles dispersed therein.

[0043] 2. The formulation of aspect 1, wherein the biocompatible polymer is comprised of polylactic glycolic acid (PLGA).

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- [0044] 3. The formulation of any of aspects 1 and 2, further comprising:
- [0045] a flavoring agent in the gel.
- [0046] 4. The formulation of any of aspects 1 to 3, further comprising a compound which generates heat via an exothermic reaction.
- [0047] 5. The formulation of any of aspects 1 to 4, wherein the reverse transcriptase inhibitor is present in an amount in the range of 100 mg to 600 mg and wherein the reverse transcriptase inhibitor is selected from the group consisting of Zidovudine, Didanosine, Zalcitabine, Stavudine, Lamivudine, Abacavir, Emtricitabine, Entecavir, Apricitabine, Tenofovir, Adefovir, Efavirenz, Nevirapine, Delavirdine, Etravirine.
- [0048] 6. The formulation of any of aspects 1 to 5, wherein the flavoring agent is a flavor selected from the group consisting of lemon, mint, cherry, strawberry, bubble gum, pina colada and chocolate.
- [0049] 7. The formulation of any of aspects 1 to 6, wherein the compound which generates heat is selected from the group consisting of propylene glycol, polyethylene glycol, hydroxypropyl cellulose, and lactic acid, and wherein the reverse transcriptase inhibitor is tenofovir and is present in an amount of 300 mg $\pm$ 10%.
- [0050] 8. The formulation of any of aspects 1 to 7, wherein the particles comprise:
- [0051] a first group of spherical particles comprising 100 or more particles wherein each particle of the first group has the same diameter as other particles in the first group with a margin of error of $\pm$ 10% or less;
- [0052] a second group of spherical particles comprising 100 or more particles wherein each particle of the second group has the same diameter as other particles in the second group with a margin of error of $\pm$ 10% or less;
- [0053] wherein particles of the first group dissolve at a rate which is faster than a rate at which the particles of the second group dissolve and the formulation provides therapeutic levels of tenofovir to a target area.
- [0054] 9. The formulation of any of aspects 1 to 8, wherein the particles further comprise:

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- [0055] a third group of spherical particles comprising 100 or more particles wherein each particle of the third group has the same diameter as other particles in the third group with a margin of error of $\pm 10\%$ or less;
- [0056] wherein particles of the third group dissolve at a rate different from a rate at which the particles of the first and second groups dissolve.
- [0057] 10. The formulation of any of aspects 1 to 9, further comprising:
- [0058] a flavoring agent selected from the group consisting of lemon, mint, cherry, strawberry, bubble gum, pina colada and chocolate; and
- [0059] a compound which generates heat which is selected from the group consisting of propylene glycol, polyethylene glycol, hydroxypropyl cellulose, and lactic acid.
- [0060] 11. The formulation of any of aspects 1 to 10, wherein the particles further comprise:
- [0061] a plurality of additional groups of spherical particles comprising 100 or more particles wherein the particles of each additional group has the same diameter as other particles in that group with a margin of error of $\pm 20\%$ or less;
- [0062] wherein particles of each additional group dissolve at a rate different from a rate at which the particles of other groups dissolve.
- [0063] 12. The formulation of any of aspects 1 to 11
- [0064] wherein the second group of particles have 1,000 square centimeters or more of surface area per 0.1cm^3 of total particle volume per group of particles more than the first group of particles; and
- [0065] wherein the third group of particles have 2,000 square centimeters or more of surface area per 0.1cm^3 of total particle volume per group of particles more than the second group of particles.
- [0066] 13. The formulation of any of aspects 1 to 12
- [0067] wherein the second group of particles have 5,000 square centimeters or more of surface area per 0.1cm^3 of total particle volume per group of particles more than the first group of particles; and

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- [0068] wherein the third group of particles have 10,000 square centimeters or more of surface area per 0.1cm^3 of total particle volume per group of particles more than the second group of particles.
- [0069] 14. The formulation of any of aspects 1 to 13, wherein the particles of each group dissolve at a rate per unit of time which is different from a rate of dissolution of any other of the groups of particles by an amount of about 25% or more.
- [0070] 15. The formulation of any of aspects 1 to 14, wherein the spherical particles in each group have a diameter in a range of from about 40 micrometers to about 2 micrometers.
- [0071] 16. The formulation of any of aspects 1 to 15, wherein the spherical particles in each group have a diameter in a range of from about 30 micrometers to about 4 micrometers.
- [0072] 17. The formulation of any of aspects 1 to 16,
- [0073] wherein the second group of particles have 1,000 square centimeters or more of surface area per 0.1cm^3 of total particle volume per group of particles more than the first group of particles; and
- [0074] wherein the third group of particles have 2,000 square centimeters or more of surface area per 0.1cm^3 of total particle volume per group of particles more than the second group of particles.
- [0075] 18. The formulation of any of aspects 1 to 17,
- [0076] wherein the second group of particles have 5,000 square centimeters or more of surface area per 0.1cm^3 of total particle volume per group of particles more than the first group of particles; and
- [0077] wherein the third group of particles have 10,000 square centimeters or more of surface area per 0.1cm^3 of total particle volume per group of particles more than the second group of particles.
- [0078] 19. Another aspect of the invention is in a use or method of improving patient compliance, comprising:

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- [0079] mixing a plurality of particles comprised of tenofovir and a biocompatible polymer with a pharmaceutically acceptable gel to provide a dispersion of particles in the gel;
- [0080] placing the dispersion of particles on a tissue surface; and
- [0081] allowing that particle to dissolve and release tenofovir.
- [0082] 20. The use or method of aspect 19, wherein the gel further comprises:
- [0083] a flavoring agent selected from the group consisting of lemon, mint, cherry, strawberry, bubble gum, pina colada and chocolate; and
- [0084] a compound which generates heat which is selected from the group consisting of propylene glycol, polyethylene glycol, hydroxypropyl cellulose, and lactic acid.
- [0085] 21. Another aspect of the invention is a drug formulation capsule, comprising:
- [0086] a polymeric biocompatible capsule; and
- [0087] a group of particles comprised of a reverse transcriptase inhibitor and a pharmaceutically acceptable carrier; and
- [0088] a second group of particles comprised of a reverse transcriptase inhibitor and a pharmaceutically acceptable carrier;
- [0089] wherein the particles within the first group of particles are substantially identical to each other and particles within the second group of particles are substantially identical to each other and different from particles in the first group, wherein the first group of particles provides for immediate release of the reverse transcriptase inhibitor and the second group of particles provides for controlled release of the reverse transcriptase inhibitor over a period of time from 24 hours to 7 days.
- [0090] 22. A drug formulation capsule of aspect 21, wherein the reverse transcriptase inhibitor is present in an amount in the range of 100 mg to 600 mg and wherein the reverse transcriptase inhibitor is selected from the group consisting of Zidovudine, Didanosine, Zalcitabine, Stavudine, Lamivudine, Abacavir, Emtricitabine, Entecavir, Apricitabine, Tenofovir, Adefovir, Efavirenz, Nevirapine, Delavirdine, Etravirine.

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- [0091] 23. A drug formulation capsule of aspect 21, wherein the flavoring agent is a flavor selected from the group consisting of lemon, mint, cherry, strawberry, bubble gum, pina colada and chocolate.
- [0092] 24. A drug formulation capsule of aspect 21, wherein the compound which generates heat is selected from the group consisting of propylene glycol, polyethylene glycol, hydroxypropyl cellulose, and lactic acid, and wherein the reverse transcriptase inhibitor is tenofovir and is present in an amount of 300 mg $\pm$ 10%.
- [0093] These and other aspects of various embodiments of the invention will become apparent to those persons skilled in the art upon reading the details of the devices and methods as more fully described below.

BRIEF DESCRIPTION OF THE DRAWINGS

- [0094] The invention is best understood from the following detailed description when read in conjunction with the accompanying drawings. It is emphasized that, according to common practice, the various features are schematic and of the drawings are not to-scale. On the contrary, the dimensions of the various features are schematic and arbitrarily expanded or reduced for clarity. Included in the drawings are the following figures:
- [0095] Figure 1 is a schematic view of a spray drying device which produces particles of random sizes and shapes.
- [0096] Figure 2 is a schematic view of an embodiment of an extrusion device used to create spherical particles of substantial uniform size and spherical shape.
- [0097] Figure 3 is a schematic view of an embodiment of an extrusion device used to create spherical coated particles of substantial uniform size and spherical shape.
- [0098] Figure 4 is a schematic graph of time versus (amount of a compound dissolved minus the amount eliminated) for a single particle or group to substantially identical particles.
- [0099] Figure 5 is a schematic graph of time versus (amount of a compound dissolved minus the amount eliminated) for two different particles or two different groups of particles (solid and dashed lines) where the particles within a given group are

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substantially identical and also showing the combined effect of the two groups (dotted lines).

[00100] Figure 6 is a schematic graph of time versus (amount of a compound dissolved minus the amount eliminated) for three different particles or three different groups of particles where the particles within a given group are substantially identical and also showing the combined effect of the three groups.

[00101] Figure 7 is a schematic diagram showing a proposed drug release rate of the invention as compared with immediate release tenofovir powder.

DETAILED DESCRIPTION OF THE INVENTION

[00102] Before the present formulations, devices and methods are described, it is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[00103] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

[00104] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those

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described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

[00105] It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a controlled release sphere" includes a plurality of such spheres and reference to "the screw" includes reference to one or more screws and equivalents thereof known to those skilled in the art, and so forth.

[00106] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

DEFINITIONS

[00107] Reverse transcriptase inhibitors (RTIs) are compounds which block reverse transcriptase's enzymatic function and prevent completion of synthesis of the double-stranded viral DNA, thus preventing HIV from multiplying. When HIV infects a cell, reverse transcriptase copies the viral single stranded RNA genome into a double-stranded viral DNA. The viral DNA is then integrated into the host chromosomal DNA, which then allows host cellular processes, such as transcription and translation to reproduce the virus. The RTIs block the enzyme function.

[00108] A similar process occurs with other types of viruses. The hepatitis B virus, for example, carries its genetic material in the form of DNA, and employs a RNA-dependent DNA polymerase to replicate. Some of the same compounds used as RTIs can also block HBV replication; when used in this way they are referred to as polymerase inhibitors.

[00109] Reverse transcriptase inhibitors come in three forms: Nucleoside analog reverse-transcriptase inhibitors (NARTIs or NRTIs), Nucleotide analog reverse-

transcriptase inhibitors (NtARTIs or NtRTIs), and Non-nucleoside reverse-transcriptase inhibitors (NNRTIs).

[00110] The mode of action of NRTIs and NtRTIs is essentially the same; they are analogues of the naturally occurring deoxynucleotides needed to synthesize the viral DNA and they compete with the natural deoxynucleotides for incorporation into the growing viral DNA chain. However, unlike the natural deoxynucleotides substrates, NRTIs and NtRTIs lack a 3'-hydroxyl group on the deoxyribose moiety. As a result, following incorporation of an NRTI or an NtRTI, the next incoming deoxynucleotide cannot form the next 5'-3' phosphodiester bond needed to extend the DNA chain. Thus, when an NRTI or NtRTI is incorporated, viral DNA synthesis is halted, a process known as chain termination. All NRTIs and NtRTIs are classified as competitive substrate inhibitors.

[00111] In contrast, NNRTIs have a completely different mode of action. NNRTIs block reverse transcriptase by binding at a different site on the enzyme, compared to NRTIs and NtRTIs. NNRTIs are not incorporated into the viral DNA but instead inhibit the movement of protein domains of reverse transcriptase that are needed to carry out the process of DNA synthesis. NNRTIs are therefore classified as non-competitive inhibitors of reverse transcriptase.

[00112] Nucleoside analog reverse-transcriptase inhibitors (NARTIs or NRTIs) compose the first class of antiretroviral drugs developed. In order to be incorporated into the viral DNA, NRTIs must be activated in the cell by the addition of three phosphate groups to their deoxyribose moiety, to form NRTI triphosphates. This phosphorylation step is carried out by cellular kinase enzymes.

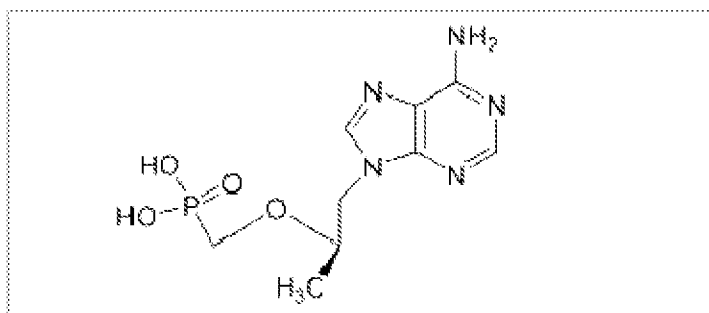
[00113] Zidovudine, also called AZT, ZDV, and azidothymidine, has the trade name Retrovir. Zidovudine was the first antiretroviral drug approved by the FDA for the treatment of HIV.

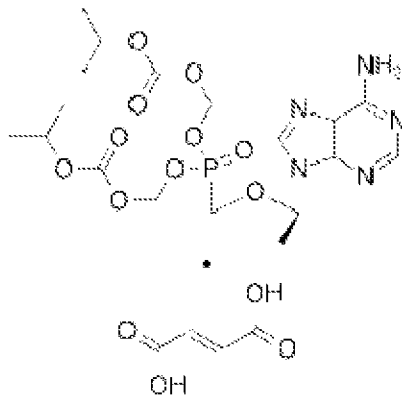
[00114] Didanosine, also called ddI, with the trade names Videx and Videx EC, was the second FDA-approved antiretroviral drug. It is an analog of adenosine.

[00115] Zalcitabine, also called ddC and dideoxycytidine, has the trade name Hivid. This drug has been discontinued by the manufacturer.

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- [00116] Stavudine, also called d4T, has trade names Zerit and Zerit XR.
- [00117] Lamivudine, also called 3TC, has the trade name Zeffix and Epivir. It is approved for the treatment of both HIV and hepatitis B.
- [00118] Abacavir, also called ABC, has the trade name Ziagen, is an analog of guanosine.
- [00119] Emtricitabine, also called FTC, has the trade name Emtriva (formerly Coviracil). Structurally similar to lamivudine, it is approved for the treatment of HIV and undergoing clinical trials for hepatitis B.
- [00120] Entecavir, also called ETV, is a guanine analog that has the trade name Baraclude. Though not currently approved as an HIV drug, entecavir is approved for the treatment of hepatitis B.
- [00121] Apricitabine, also called ATC. As of 2009, this drug is undergoing Phase-III evaluation, and if successful may achieve FDA approval in 2011.
- [00122] Normally, nucleoside analogs are converted into nucleotide analogs by the body. Taking nucleotide analog reverse-transcriptase inhibitors (NtARTIs or NtRTIs) directly allows conversion steps to be skipped.
- [00123] Tenofovir, also known as TDF is a so called 'prodrug' with the active compound deactivated by a molecular side chain that dissolves in the human body allowing a low dose of tenofovir to reach the site of desired activity. One example of the prodrug form is tenofovir disoproxil fumarate with the trade name Viread (Gilead Sciences Inc USA). It is approved in the USA for the treatment of both HIV and hepatitis B.





Tenofovir (top) and tenofovir disoproxil fumarate (bottom)

Systematic (IUPAC) name

(([(2*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-yl]oxy)methyl)phosphonic acid

[00124] Tenofovir disoproxil fumarate is a prodrug form of tenofovir. Tenofovir is also available in a fixed-dose combination with emtricitabine in a product with the brand name Truvada for once-a-day dosing. Atripla, a fixed-dose triple combination of tenofovir, emtricitabine and efavirenz, was approved by the FDA on 12 July 2006 and is now available, providing a single daily dose for the treatment of HIV.

[00125] Adefovir, also known as bis-POM PMPA, has trade names Preveon and Hepsera. It was not approved by the FDA for treatment of HIV due to toxicity issues, but a lower dose is approved for the treatment of hepatitis B.

[00126] Non-nucleoside reverse-transcriptase inhibitors (NNRTIs) are the third class of antiretroviral drugs that were developed. Examples of RTIs include Efavirenz, which has the trade names Sustiva and Stocrin. Nevirapine, which has the trade name Viramune. Delavirdine, which currently is rarely used and has the trade name Rescriptor. Etravirine which has the trade name Intelence, and was approved by the FDA in 2008. Rilpivirine which has the trade name Edurant, and was approved by the FDA in May 2011.

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[00127] Researchers have designed molecules which dually inhibit both reverse transcriptase (RT) and integrase (IN). These drugs are a type of "portmanteau inhibitors".

[00128] While NRTIs and NNRTIs alike are effective at terminating DNA synthesis and HIV replication, HIV can and eventually does develop mechanisms that confer the virus resistance to the drugs. HIV-1 RT does not have proof-reading activity, this combined with selective pressure from the drug leads to mutations in reverse transcriptase that make the virus less susceptible to NRTIs and NNRTIs. Aspartate residues 110, 185, and 186 in the reverse transcriptase polymerase domain are important in the binding and incorporation of nucleotides. The side chains of residues K65, R72, and Q151 interact with the next incoming nucleotide. Also important is L74, which interacts with the template strand to position it for base pairing with the nucleotide. Mutation of these key amino acids results in reduced incorporation of the analogs.

[00129] There are two major mechanisms of NRTI resistance. The first being reduced incorporation of the nucleotide analog into DNA over the normal nucleotide. This results from mutations in the N-terminal polymerase domain of the reverse transcriptase that reduce the enzyme's affinity or ability to bind to the drug. A prime example for this mechanism is the M184V mutation that confers resistance to lamivudine (3TC) and emtricitabine (FTC). Another well characterized set of mutations is the Q151M complex found in multi-drug resistant HIV which decreases reverse transcriptase's efficiency at incorporating NRTIs, but does not affect natural nucleotide incorporation. The complex includes Q151M mutation along with A62V, V75I, F77L, and F116Y. A virus with Q151M alone is intermediately resistant to zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), and slightly resistant to abacavir (ABC). A virus with Q151M complexed with the other four mutations becomes highly resistant to the above drugs, and is additionally resistant to lamivudine (3TC) and emtricitabine (FTC).

[00130] The second mechanism is the excision or the hydrolytic removal of the incorporated drug or pyrophosphorolysis. This is a reverse of the polymerase reaction in

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which the pyrophosphate/PPI released during nucleotide incorporation reacts with the incorporated drug (monophosphate) resulting in the release of the triphosphate drug. This ‘unblocks’ the DNA chain, allowing it to be extended, and replication to continue. Excision enhancement mutations, typically M41L, D67N, K70R, L210W, T215Y/F, and K219E/Q, are selected for by thymidine analogs AZT and D4T; and are therefore called thymidine analog mutations (TAMs). Other mutations including insertions and deletions in the background of the above mutations also confer resistance via enhanced excision.

[00131] NNRTIs do not bind to the active site of the polymerase but in a less conserved pocket near the active site in the p66 subdomain. Their binding results in a conformational change in the reverse transcriptase that distorts the positioning of the residues that bind DNA, inhibiting polymerization. Mutations in response to NNRTIs decrease the binding of the drug to this pocket. Treatment with a regimen including efavirenz (EFV) and nevirapine (NVP) typically results in mutations L100I, Y181C/I, K103N, V106A/M, V108I, Y188C/H/L and G190A/S. There are three main mechanisms of NNRTI resistance. In the first NNRTI mutations disrupt specific contacts between the inhibitor and the NNRTI binding pocket. An example of this is K103N and K101E which sit at the entrance of the pocket, blocking the entrance/binding of the drug. A second mechanism is the disruption of important interactions on the inside of the pocket. For example Y181C and Y188L result in the loss of important aromatic rings involved in NNRTI binding. The third type of mutations result in changes in the overall conformation or the size of the NNRTI binding pocket. An example is G190E, which creates a steric bulk in the pocket, leaving little or no room for an NNRTI to tightly bind.

[00132] The terms “treatment”, “treating” and the like are used herein to generally mean obtaining a desired pharmacological or physiological effect. The effect may be prophylactic in terms of completely or partially preventing an infection or disease such as an infection or symptom thereof and may be therapeutic in terms of partially or completely curing a disease and/or adverse effect attributed to the disease or infection.

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“Treatment” as used herein covers inhibiting any viral infection such as an HIV infection in a human, and includes:

- [00133] (a) preventing the infection from occurring or developing in the subject which may be predisposed to the infection but has not yet been diagnosed as having it;
- [00134] (b) inhibiting the infection, i.e. arresting its development; or
- [00135] (c) relieving the infection, i.e. causing regression of the infection.

Treatment may be specifically directed towards treating patients who may have intercourse with an individual who is already infected with HIV in order to prevent infection of the patient.

FORMULATIONS

[00136] In one form a formulation of the invention might be comprised of two groups of particles. The particles within each group may have the same size and shape e.g. spherical and vary in size $\pm 10\%$. However, the particles in the first group will be different from the particles in the second group in a manner which results in the first group dissolving at a rate which is faster than the particles in the second group. The particles are comprised of a biocompatible polymer and a drug which is a reverse transcriptase inhibitor such as a tenofovir. Other groups of particles and particles of different sizes may be added to such a formulation in order to provide variations on the release profile in order to get a release rate similar to that shown in Figure 7. The object is to obtain release at a low, but therapeutically effective level at the target area over a sufficiently long period of time (1-7 days) so as to prevent infection and to avoid reaching toxic levels shown in Figure 7.

[00137] The formulation may be designed in a form of a capsule. The capsule incorporates 100 to 600 mg of a reverse transcriptase inhibitor drug which may be tenofovir. The capsule may include groups of particles and a gel or simply include the particles without the gel where the drug is present in an amount of about 300 mg $\pm 10\%$. The capsule and particles may be designed such that essentially no drug is released immediately upon administration, and thereafter when the capsule dissolves drug is released in pulses (see Figure 7) beginning with immediate release particles and

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continuing to controlled release particles so as to provide a therapeutic level of the drug locally in the vagina over a period of time of from 24 hours to about 7 days.

[00138] In addition to the basic formulation may include any mixtures of particles in a solution, in a biocompatible gel or combination of the solution and gel with two or more reverse transcriptase inhibitors therein. More specifically, the formulation may be comprised of the particles included within a separate sealed packet. That packet may be opened just prior to use and added to an aqueous solution. In another formulation of the invention particles or the groups of particles contained within the sealed packet are opened just prior to administration and added to a biocompatible gel. The particle formulations are mixed into the gel so that the particles are evenly distributed throughout the gel. Thereafter, the formulation comprised of the gel having particles dispersed therein is administered to a patient such as by injecting the formulation from a syringe.

[00139] In yet another embodiment the particles or groups of particles contained within the packet or packets are removed from the packet just prior to use and added to the aqueous solution as described above. Further, just prior to administration that aqueous solution is intermixed with a biocompatible gel such as FlosealTM. The particles and solution are thoroughly mixed with a compatible gel such as FlosealTM. A combination of particles, thrombin solution and FlosealTM may be thoroughly mixed within a syringe or other appropriate container. After dispersing the solution and particles throughout the gel the formulation is administered to a vagina prior to intercourse.

[00140] Those skilled in the art will understand that the drug release profile can be affected by the size and number of the particles as described below and further affected by the amount of solution and gel. Those skilled in the art having this disclosure before them will understand that it is preferable to create formulations which have desired drug release profiles shown within Figures 7 and 8 and provide an efficacious but non-toxic dose over a sufficiently long period to prevent infection. More specifically, the drug which may be a reverse transcriptase inhibitor such as tenofovir is preferably not administered systemically but rather locally. Further, it is administered in an amount so as to obtain a therapeutic level but not a toxic level 30 mcg/ml $\pm$ 25

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mcg/ml. Still further, the therapeutic level is preferably maintained over a sufficiently long period of time so as to prevent infection (over 24 hours). Still further, low levels of drug release over long periods of time as shown in Figure 7 are preferred.

[00141] Those skilled in the art will understand that any of the embodiments of the invention described above can be further supplemented by adding some quick release drug which may be a powdered form of a drug such as a powdered form of a reverse transcriptase inhibitor such as tenofovir. Thus, the powdered drug can be combined with the particles or groups of particles in solution, or combined with the particles, solution and gel. Those skilled in the art will understand that the various components of the formulation can be intermixed in a manner so as to evenly disperse the components throughout the formulation or the different components can be added separately to a vagina prior to intercourse. With these various formulations in mind those skilled in the art should consider the mathematics of the controlled release particles as described further below.

MATHEMATICS OF CONTROLLED RELEASE PARTICLES

[00142] The formulation packets are comprised of particles or groups of particles based on mathematics. For any given particle having a given amount of surface area the rate of dissolution will decrease as the particle dissolves and the total available surface area decreases. Thus, a spherical particle with two square units of available surface area which dissolves at a rate of X per unit of time will be dissolving at a rate of X/2 per unit of time once the particle has dissolved so that it has one square unit of available surface area. This assumes a constant environment unaffected by the dissolution.

[00143] By combining two different particles each comprised of the same material but of a different size the combined rate of the two particles together is different from either particle by itself. The combined rate of a small and a large particle is slower than two large particles and faster than two small particles. Formulations of the invention are comprised of two or more groups of particles having a diameter of 2 to 40 microns and with 100 or more particles per group. The different groups of particles may include the same or different numbers of particles.

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[00144] A particle with a large available surface area has a more rapid dissolution rate than a particle with a small available surface area. However, assuming the same total volume in two groups of particles the group of smaller particles has a faster dissolution rate than the group of larger particles because the group of smaller particles will have a larger available surface area than the group of larger particles.

[00145] It is often desirable to deliver a predetermined amount of compound (such as a drug) to a system (such as a human) at a rate which maintains the compound in the system at a desired level over a desired period of time. When the total amount (weight and volume) is fixed the rate of dissolution is dictated by the available surface area. One spherical particle with a given total volume will present approximately half the surface area as ten particles with the same combined volume as the one particle.

[00146] Each time the number of particles is increased by a multiple of ten (and the combined volume remains constant) the total available surface area approximately doubles (see Table 1). The following provides specific examples of how the total available surface area increases as the same total volume (e.g. a drug) is included in larger numbers of spheres.

[00147] Formulations and/or devices coated with a formulation of the invention may include some reverse transcriptase inhibitor by itself (no polymer sphere) such as an tenofovir for immediate release to provide a fast antiviral effect in the surrounding area. Further, greater numbers of groups of different particles can increase the duration time the drug is released and decrease changes in the concentration of the drug in the surrounding areas over time. Further, the multiple groups can be effective in keeping the concentration in the desired range – high enough to be therapeutic but low enough so as to not be toxic. Thus, 2 or more, 3 or more, 4 or more or 5 or more groups can be used to maintain the desired therapeutic level over time – see Figures 4, 5 and 6.

SPECIFICS OF PARTICLE SIZES

[00148] Assuming a packet of formulation will contain a total volume of 2 cubic centimeters the size a single sphere which will hold a 2cc volume can be readily calculated using the formula for the volume of a sphere as follows:

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[00149] Volume of a sphere = $(4/3) \pi r^3$ if the volume of a sphere is 2cc then

[00150] $2 \text{ cc} = (4/3) \pi r^3$

[00151] $2 = (4/3) 3.14159 r^3$

[00152] $2 = 4.1887867 r^3$

[00153] $0.477645 = r^3$

[00154] $0.781592 \text{ cm} = r$

[00155] $r = 7,815 \text{ micrometers}$

[00156] $\text{diameter} = d = 2r = 15,630 \text{ micrometers}$

[00157] The formula for the surface area of a sphere is $4\pi r^2$. Because "r" was found to be 0.781592 cm the surface area = $4(3.14159)(0.781592) = 9.8217 \text{ cm}^2$.

[00158] The formula for the volume of a sphere can be readily modified to determine the volume of any number of spheres "n" needed to make a total volume of 2 cubic centimeters.

[00159] $2 \text{ cc} = n(4/3) \pi r^3$

[00160] This formula was solved above for "n" equals "1" and can be solved for any "n." For example, when "n" is 10 the formula becomes

[00161] $2 \text{ cc} = 10(4/3) \pi r^3$

[00162] $2 \text{ cc} = 10(4/3) 3.14159 r^3$

[00163] $2 \text{ cc} = 41.887867 r^3$

[00164] $0.0477645 = r^3$

[00165] $0.362783 \text{ cm} = r$

[00166] $r = 3627 \text{ micrometers}$

[00167] $d = 7254 \text{ micrometers}$

[00168] The volume of each sphere is 0.2 cm^3 and the surface area of each sphere is 1.65388 cm^2 . Thus, the total volume of the 10 spheres remains the same (i.e. 2cc) but the surface area of all 10 spheres is 16.5 cm^2 as compared to 9.8217 cm^2 when "n" was one.

[00169] When "n" equals 100 the radius "r" can be solved for and found to be 0.1684cm with the volume of each of the 100 spheres being 0.02 cm^3 . The surface area of each sphere is 0.3563 cm^2 and the combined surface area of all 100 spheres is 35.63 cm^2 --

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the combined volume remains the same at 2cm^3 . The equations for the surface area and volume can be used to solve for the radius "r" and diameter "d" of any number of spheres "n" which equal a total volume of 2cm^3 and the results are provided below.

TABLE 1
Total volume is 2cm^3

N	r(micrometers)	D	Surface area (cm^2)	<u>Surface Area</u> <u>Volume</u> (cm^{-1})
1	7815	15,630	9.8217	4.91085
10	3627	7,254	16.5	8.25
100	1684	3,378	35.63	17.815
1,000	781	1,562	76.766	38.383
10,000	362	724	165	82.5
100,000	168	336	356	178
1,000,000	78	156	768	384
10,000,000	36	72	1,653	826.5
100,000,000	16.8	33.6	3,563	1781.5
1,000,000,000	7.8	15.6	7,677	3838.5
10,000,000,000	3.6	7.2	16,539	8269.5
100,000,000,000	1.6	3.2	35,631	17815.5

[00170] From the above it can be seen that when "n" is increased by a factor of 10 and total combined volume is maintained constant at 2.0 and the combined surface area of all of the spheres increases by approximately a factor of 2 for each increase of 10x for n.

[00171] Although the surface area approximately doubles as "n" increases by a factor of ten the absolute effect of the doubling is small when "n" is increased from 1 to 10 to 100. Specifically, the increase in surface area from 9.8 to 16.5 is only an increase of 6.7cm^2 and from 16.5 to 35.6 is only an increase of 19.1cm^2 . However, when "n" increases from 10^9 to 10^{10} the surface area increases from 7677 to 16,539 resulting in

an increase of 8,862cm². When "n" increases from 10¹⁰ to 10¹¹ the surface area increases from 16,539 to 35,631 resulting in an increase of 18,992cm².

[00172] However, this differential in surface area between groups will be less when the total volume is less. This differential is based on a total volume of 2cm³ which is a large dose. The dose may be 1cm³, 0.1cm³, 0.01cm³, 0.001cm³ or less. With smaller volumes the total surface area differential between groups will be less.

[00173] For "n" at the extremes of the calculations provided above the gross increase in surface area is as follows:

TABLE 2

N	gross increase in surface area (cm ²)
1 to 10	6.7
10 to 100	19.1
10 ⁹ to 10 ¹⁰	8,863
10 ¹⁰ to 10 ¹¹	18,992

[00174] The larger the available surface area the faster the rate of dissolution of the solute drug assuming the solvent is not saturated. In nearly all situations the solute drug will only be administered to the surrounding environment of the solvent (e.g. tissue such as bone) in relatively small amounts. Accordingly, the solvent never approaches saturation and the circulatory systems aids in refreshing the solvent over time.

[00175] Formulations of the invention are described and claimed here and such formulations may have two, three or a plurality of different groups of particles therein. The formulation suspension may be created where a first group has a first surface area and a second group has 1,000 square centimeters or more surface area than the first group or e.g. 2,000 or more; 5,000 or more; or 10,000 or more square centimeters of surface area per 0.1cm³ of total volume per group of particles more than the surface area of the first group. Formulations of suspensions of particles may be created

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whereby a plurality of different groups are present and the total surface area of any one group different from the total surface area of any other group by a desired amount e.g. 1,000; 2,000; 3,000; 4,000; 5,000; and 10,000 or more square centimeters of surface area per 0.1cm^3 of total volume per group of particles.

[00176] Using data such as generated in Table 1 and the results of Table 2 a formulation of the invention can be created which provides a desired release profile. The desired release profile can be understood by reference to Figure 7 which is a schematic diagram showing areas where a given concentration of a reverse transcriptase inhibitor might be obtained over time with different groups of particles. Figure 7 shows how therapeutic levels can be maintained over a relatively long period of time.

[00177] It will be understood that the formulation and amount of drug can vary depending on the particular reverse transcriptase inhibitor and the polymer used. Further, the shape and size of the particles will effect the dissolution time as well as the particle configuration. More particularly, the particle may be comprised of polymer intermixed with the drug or have the drug encapsulated within a polymer. There will also be some variation depending on the patient in that patient's with poor circulation provide a different environment for the particles as compared to patient's with normal circulation.

[00178] The solvent or surrounding environment into which the drug is administered can be assumed to be known within the vagina. Thus, the unknown that remains is the rate of dissolution of a particle of known size in a given solvent. After calculating the rate of release "R" (weight or volume dissolved per unit of time) for a known particle size the rate of dissolution of other particle sizes with different available surface areas can be calculated. Assuming all the particles of a group of particles are spherical and also assuming that the particles in a given group of particles all have substantially the same size (available surface area), the rate of dissolution of a group of particles can be readily determined. Using this information a formulation can be created with different groups or types of particles wherein each group of particles has a known drug release profile within the environment the formulation is delivered to. The formulation preferably comprises a number of different groups which release drug at different rates

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and/or times and provide a desired drug release profile, e.g. substantially constant levels in the surrounding area over a therapeutically effective time period.

[00179] Calculations are provided below in Tables 3, 4 and 5 respectively for total volumes of 1cm^3 , 0.5cm^3 and 0.1cm^3 which are volume sizes that might be used for typical dosages of orally administered pharmaceutically active compounds.

TABLE 3
Total volume is 1 cm^3

number of spheres	radius (micrometers)	Diameter (micrometers)	Surface area (cm^2)	<u>Surface area</u> Volume (cm^{-1})
1	6203.5	12407.0	4.84	4.8
10	2879.4	5758.8	10.42	10.4
100	1336.5	2673.0	22.45	22.4
1,000	620.4	1240.7	48.36	48.4
10,000	287.9	575.9	104.19	104.2
100,000	133.7	267.3	224.47	224.5
1,000,000	62.0	124.1	483.60	483.6
10,000,000	28.8	57.6	1041.88	1041.9
100,000,000	13.4	26.7	2244.66	2244.7
1,000,000,000	6.2	12.4	4835.98	4836.0
10,000,000,000	2.9	5.8	10418.79	10418.8
100,000,000,000	1.3	2.7	22446.61	22446.6

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TABLE 4
Total volume is 0.5 cm³

number of spheres	Radius (micrometers)	diameter (micrometers)	Surface area (cm ²)	<u>Surface area</u> Volume
1	4923.7	9847.5	3.05	6.1
10	2285.4	4570.8	6.56	13.1
100	1060.8	2121.6	14.14	28.3
1,000	492.4	984.7	30.46	60.9
10,000	228.5	457.1	65.63	131.3
100,000	106.1	212.2	141.40	282.8
1,000,000	49.2	98.5	304.65	609.3
10,000,000	22.9	45.7	656.34	1312.7
100,000,000	10.6	21.2	1414.05	2828.1
1,000,000,000	4.9	9.8	3046.47	6092.9
10,000,000,000	2.3	4.6	6563.43	13126.9
100,000,000,000	1.1	2.1	14140.48	28281.0

TABLE 5
Total volume is 0.1 cm³

number of spheres	radius (micrometers)	Diameter (micrometers)	Surface area (cm ²)	<u>Surface area</u> Volume
1	2879.4	5758.8	1.04	10.4
10	1336.5	2673.0	2.24	22.4
100	620.4	1240.7	4.84	48.4
1,000	287.9	575.9	10.42	104.2
10,000	133.7	267.3	22.45	224.5
100,000	62.0	124.1	48.36	483.6
1,000,000	28.8	57.6	104.19	1041.9
10,000,000	13.4	26.7	224.47	2244.7
100,000,000	6.2	12.4	483.60	4836.0

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number of spheres	radius (micrometers)	Diameter (micrometers)	Surface area (cm ²)	<u>Surface</u> <u>area</u> Volume
1,000,000,000	2.9	5.8	1041.88	10418.8
10,000,000,000	1.3	2.7	2244.66	22446.6
100,000,000,000	0.6	1.2	4835.98	48359.8

PARTICLE FORMATION METHODOLOGY

[00180] Particles and coated particles can be produced via any available technology.

Referring to Figure 1, cylindrical tube 1 is shown in fluid connection with a liquid source 2 which can supply liquid 3 to the tube 1. The liquid 3 exits the tube 1 from an exit opening which can be any configuration but is preferably circular and has a diameter D. The liquid 3 exits the opening 4 and forms a stream which breaks into segments 5 and eventually forms partial spheres 6 and then spheres 7 which are substantially equal in size and shape. The spheres 7 could be used in creating a group of particles for attachment to a device such as a surgical screw. Different size spheres from different sized tubes 1 could create different groups of spheres as needed for a desired dissolution profile.

[00181] The processing of Figure 1 can stop at the formation of the particles 7.

However, in order to attempt to obtain a dissolution profile which achieves a longer steady state level of the desired compound a coating is often used. The coating source 8 creates a spray 9 of a coating material which is brought into contact with and sticks to particles 10, 11 and 12 often in different amounts. Further, two particles 13 may become coated together or three or more particles 14 may become coated together.

[00182] The result is a random mixture of particles coated to different degrees and combined with different numbers of other particles. Coated particles of this type could be used if they provide the desired level of drug at the target site over the desired period of time. The coating material can be mixed with rather than sprayed on the particles and a similar random mixture of coated particles and coated groups of particles will result. The random mixture has some advantages. It can provide a

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greater range of release rates than a single type of particle. The greater range of release rates may provide a release profile which is desirable. However, a degree of trial and error is required in producing a desired release profile. Further, great care must be taken once the desired profile is obtained in repeating all preparation steps precisely from batch to batch. Otherwise, each new batch of formulation produced will have a different release profile.

[00183] The process for producing particles 7 as shown in Figure 1 has yet another disadvantage or limitation. Specifically, the diameter D of the tube 1 dictates that the diameter of the particles 7 formed will be approximately $D \times 1.89$ (Rayleigh, "On the instability of jets", Proc. London Math. Soc., 4-13, 1878). Thus, when attempting to make very small particles (e.g. less than 20 micrometers) the inside diameter of the tube 1 must be very small. Not only is it difficult to manufacture tubes with such a small diameter but the narrower tubes tend to clog easily. These problems can be solved by using a different technology for producing particles and coated particles as shown in Figures 2 and 3.

[00184] Figure 2 shows a tube 21 supplied by a liquid source 22. The liquid 23 flows out of the exit 24. The liquid 23 stream is focused to a narrowed stable jet 25 by a gas 26 provided by the gas source 27 flowing into a pressure chamber 28 and out of an exit orifice 29. The jet 25 disassociates into segments 30 which form spheres 31 in the same manner in which the stream of liquid 3 forms the spheres 7 shown in Figure 1. However, the spheres 31 have a diameter which is $1.89 \times$ the diameter D_j of the jet and not $1.89 \times$ the diameter D of the tube 21. The diameter of the jet 25 (D_j) is substantially smaller than the diameter D of the tube 21. Thus, the system of Figure 2 can be used to make very small particles as compared to the system of Figure 1 without clogging the exit 24 of the tube 21 because the diameter D of the tube 21 can remain large - and without clogging the exit orifice 29 of the pressure chamber 28 because the jet 25 exits the orifice 29 surrounded by the gas 26.

[00185] The particles 31 can be coated using a spray on coating as shown in Figure 1. However, similar problems occur as described above with reference to Figure 1. The particles 31 can be used without any coating. Groups of particles can be combined to

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provide a desired dissolution profile. The small size of the particles provides certain advantages as shown in Tables 1-5. Particles in a size range of 1-20 micrometers can not be easily produced in a system as shown in Figure 1 and particles in this size range provide the greatest differences in surface areas - see Tables 1-5 and Table 2 in particular. However, the particles themselves (without a coating) are limited in terms of the dissolution profile they can produce particularly when the total volume of the particles in a formulation is limited. Thus, a coating is preferred and a preferred means of obtaining such is shown in Figure 3.

[00186] The system schematically shown in Figure 3 includes a tube 41 in fluid connection with a liquid source 42 which supplies liquid 43 to the cylindrical channel of the tube 41. A tube 44 is concentrically positioned around the tube 41 and is in fluid connection with a coating source 45. The exit opening 46 of the tube 41 and the exit opening 47 of the tube 44 are both positioned inside of a pressure chamber 48. The chamber 48 is in fluid connection with the gas source 49 which flows out of the exit orifice 50 of the chamber 48. The gas 51 focuses the streams of liquid 43 and coating 52 into a stable jet 53. The jet 53 disassociates into segmented streams 54 of liquid 43 concentrically surrounded by coating 52. The segmented streams 53 form spheres 55. The spheres 55 are comprised of a liquid 43 center surrounded by a polymeric (e.g. PLGA) coating 52. The spheres 55 are preferably very small, e.g. a diameter of less than 50 μ m, preferably less than 20 μ m and more preferably about 10 μ m. The smaller the particles the more readily evaporation will take place which will cure or solidify the coating 52.

[00187] An energy source 56 may be used to direct energy 57 onto the particles 55 to enhance the rate of curing, hardening, evaporation, etc. The energy 57 may be any type of energy including heat, forced air, I.R. or U.V. light etc. alone or in combination. Some polymer materials are designed to be cured using a particular frequency of light. The light can be directed, focused and/or intensified using lenses, mirrors and the like to obtain a desired result. The particles 55 could be produced and dispersed in a biocompatible gel and applied to bone and/or an orthopedic implant.

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- [00188] The coated particles 55 can include any liquid 43 coated with any coating material 52. However, in accordance with the present invention it is preferable that the liquid 43 be comprised of a pharmaceutically active drug which is preferably a reverse transcriptase inhibitor and more preferably a tenofovir. Further, the coating material can be comprised of any type of material which can be cured, dried or fixed in any fashion in order to form an outer spherical coating around the center. However, it is preferable that the coating material be comprised of a polymer material and more preferable if the polymer material is quickly and readily curable and is a material which is commonly accepted as useful as a carried material in controlled release formulations used in pharmaceutical applications. A number of such polymer materials are disclosed within the patents and publications described below.
- [00189] U.S. Patent 3,773,919 describes creating slow release formulations producing a steady release of drug in the bloodstream by employing polylactide-drug mixtures in the dosage form. The inventors describe using a chemical based microencapsulation procedure for forming precipitates of the polylactide-drug mixtures suitable for injection. They discuss many potential applications for their invention including the administration of morphine.
- [00190] U.S. Patent 4,942,035 describes using PLGA polymer as an excipient allowing formulations to be created to facilitate the controlled release of polypeptide active drugs into solutions.
- [00191] U.S. Patent 5,514,380 describes modifying the cross-linking in PLGA polymer in order to obtain more controllable release profiles.
- [00192] U.S. Patent 5,543,158 describes potential benefits of using PLGA polymer with pharmaceutically active drug to create particles in a very small size range to minimize incorporation of the injected formulation into the patient's macrophages which would result in inactivation of the drug.
- [00193] U.S. Patent 5,650,173 describes an emulsion system for creating particles of PGLA and active drug suitable for injection.

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- [00194] U.S. Patent 5,654,008 describes a technique for combining PLGA and active drug into microparticles suitable for injection by using an emulsion system created using a static mixer.
- [00195] U.S. Patent 5,759,583 describes using a quaternary ammonium surfactant as an excipient to facilitate the creation of PLGA drug combinations suitable for injection to create a controlled release formulation.
- [00196] U.S. Patent 5,912,015 describes using metal cations as release modulators in the injectable drug formulation comprising PLGA and active drug.
- [00197] U.S. Patent 5,916,598 describes using emulsion systems and solvent extraction techniques as tools for creating microparticles comprised of PLGA and active drug for sustained release formulations.
- [00198] U.S. Patent 6,254,890 describes using PLGA to create sustained release formulations containing nucleic acids.
- [00199] Previous approaches for combining PLGA with active drug to create such controlled release formulations relied on chemical techniques for creating microparticles suitable for injection. These techniques have focused on the use of solvent systems to produce emulsions resulting in the creation of a precipitate of crystalline microparticle in an approximate size range suitable for injection. Other systems involve removing solvents used during the fabrication process. The US FDA as well as international drug regulatory authorities have drafted regulations strictly limiting the amount of residual solvent acceptable in marketed pharmaceutical preparations (ICH Harmonized Tripartite Guideline Q3C Impurities: "Guidelines for Residual Solvents").
- [00200] Additional discussion of categories of systems for controlled release may be found in Agis F. Kydonieus, Controlled Release Technologies: Methods, Theory and Applications, 1980 (CRC Press, Inc.).
- [00201] Controlled release drug delivery systems may also be categorized under their basic technology areas, including, but not limited to, rate-preprogrammed drug delivery systems, activation-modulated drug delivery systems, feedback-regulated drug delivery systems, and site-targeting drug delivery systems.

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- [00202] In rate-preprogrammed drug delivery systems, release of drug molecules from the delivery systems is "preprogrammed" at specific rate profiles. This may be accomplished by system design, which controls the molecular diffusion of drug molecules in and/or across the barrier medium within or surrounding the delivery system. Fick's laws of diffusion are often followed.
- [00203] In activation-modulated drug delivery systems, release of drug molecules from the delivery systems is activated by some physical, chemical or biochemical processes and/or facilitated by the energy supplied externally. The rate of drug release is then controlled by regulating the process applied, or energy input.
- [00204] In feedback-regulated drug delivery systems, release of drug molecules from the delivery systems may be activated by a triggering event, such as a biochemical substance, in the body. The rate of drug release is then controlled by the concentration of triggering agent detected by a sensor in the feedback regulated mechanism.
- [00205] In a site-targeting controlled-release drug delivery system, the drug delivery system targets the active molecule to a specific site or target tissue or cell. This may be accomplished, for example, by a conjugate including a site specific targeting moiety that leads the drug delivery system to the vicinity of a target tissue (or cell), a solubilizer that enables the drug delivery system to be transported to and preferentially taken up by a target tissue, and a drug moiety that is covalently bonded to the polymer backbone through a spacer and contains a cleavable group that can be cleaved only by a specific enzyme at the target tissue.
- [00206] Another controlled release dosage form is a complex between an ion exchange resin and the lipoates. Ion exchange resin-drug complexes have been used to formulate sustained-release products of acidic and basic drugs. In one preferable embodiment, a polymeric film coating is provided to the ion exchange resin-drug complex particles, making drug release from these particles diffusion controlled. See Y. Raghunathan et al., Sustained-released drug delivery system I: Coded ion-exchange resin systems for phenylpropanolamine and other drugs, J. Pharm. Sciences 70: 379-384 (1981).
- [00207] Injectable micro spheres are another controlled release dosage form. Injectable micro spheres may be prepared by non-aqueous phase separation techniques, and

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spray-drying techniques. Micro spheres may be prepared using polylactic acid or copoly(lactic/glycolic acid). Shigeyuki Takada, Utilization of an Amorphous Form of a Water-Soluble GPIIb/IIIa Antagonist for Controlled Release From Biodegradable Micro spheres, Pharm. Res. **14**:1146-1150 (1997), and ethyl cellulose, Yoshiyuki Koida, Studies on Dissolution Mechanism of Drugs from Ethyl Cellulose Microcapsules, Chem. Pharm. Bull. **35**:1538-1545 (1987).

[00208] To form a coated particle 55 the liquid 43 is forced through the channel of the tube 41. The liquid is preferably a relatively high concentration of a drug such as a reverse transcriptase inhibitor in either an aqueous or alcohol based solvent or other solvent which will quickly evaporate (e.g. ether). The exit opening 46 of the tube 41 and the exit opening 47 of the tube 44 are both positioned inside the pressure chamber 48. The coating material 52 is initially in a liquid form and is forced through the exit opening 46 of the tube 44 which is positioned concentrically around the tube 41 in a manner which causes a stream of the liquid coating material to be expelled from the opening 47 at substantially the same velocity as the liquid 43 is forced from the opening 46 of the tube 41. Accordingly, the stream of the coating material is concentrically positioned around the stream of the center liquid 43. The streams exit the openings of the two concentrically positioned tubes as a single combined stream which then disassociates into segments streams 53 which segments form the cooled spheres 55.

[00209] In order for the spheres to be made small it is effective to use the gas from the gas source 49 forced into the pressure chamber 48 in a manner which causes the gas to exit the pressure chamber 48 downstream of the concentrically positioned streams exiting the tubes 41 and 44. It is preferable for the density of the liquid 43 to be substantially the same as the liquid of the coating 52. This allows the gas from the gas source 49 to focus the concentrically positioned streams into a stable unified jet which flows out of the chamber 48 breaking up into segments and thereafter forming the spherical coated particles 55 of the coating material surrounding the center of pharmaceutically active drug.

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[00210] In accordance with the invention the gas from the gas source forms the stable jet and the diameter of the jet is substantially smaller than would be the case if the gas were not focusing the streams exiting the tubes 41 and 44. The diameter of the jet is defined by the following formula:

$$d_j \cong \left(\frac{8\rho_l}{\pi^2 \Delta P_g} \right)^{1/4} Q^{1/2}$$

[00211] wherein d_j is the diameter of the stable unified jet, $\cong$ indicates approximately equally to where an acceptable margin of error is $\pm 10\%$, ρ_l is the average density of the liquid of the jet and ΔP_g is change in gas pressure of gas surrounding the stream at a given point A at the exit and Q is the total flow rate of the stable unified jet.

[00212] By using the technology described above and shown in Figures 2 and 3 it is possible to form very small and very uniform particles. The particles may be of any size but are preferably in less than 100 micrometers in diameter, more preferably less than 50 micrometers in diameter and still more preferably less than 20 micrometers in diameter. The technology described above and shown in Figure 2 and 3 is capable of producing particles which are as small as approximately 1 micrometer in diameter and preferred devices of the invention will include particles which have a diameter of approximately 10 micrometers. The sphere forming technology can produce particles which are substantially identical in shape (spherical) and substantially identical in size $\pm 10\%$ variation in the particle diameter, more preferably $\pm 3\%$ and still more preferably $\pm 1\%$ variation in particle diameter where the particle may have a diameter as small as 1 μm or more or as large as 100 μm or more.

[00213] Those skilled in the art will understand that in addition to the tubes 41 and 44 a plurality of additional concentrically positioned tubes may be added to the system. This would make it possible to add additional coating materials or include additional active components surrounded by outer shells of coating material. An out coating of adhesive could be added so that the particles 55 have an adhesive thereon and adhere to an orthopedic implant and/or to bone. Those skilled in the art will understand that the

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system works best when the Weber Number is in a range of from about 1 to about 40 wherein the Weber Number is defined by the following equation:

$$We = \frac{\rho_g V_g^2 d}{\gamma}$$

[00214] wherein the ρ_g is the density of the gas, d is the diameter of the stable microjet, γ is the liquid-gas surface tension and V_g^2 is the velocity of the gas squared. More preferably the Weber number is in a range of about 5 to about 25.

[00215] Further, those skilled in the art will understand that it is preferable for the Ohnesorge number to be less than 1, wherein the Ohnesorge number (Oh) is defined by

$$Oh = \frac{\mu_l}{(\rho_l \gamma d)^{1/2}}$$

[00216] wherein μ_l is the velocity of the liquid, ρ_l is the density of the liquid and d is the diameter of the stable capillary microjet.

[00217] Those skilled in the art will also understand that the method for producing particles and coated particles as described above is best carried out when the difference in the pressure between the pressure chamber exit orifice is equal to or less than 20 times the surface tension of the liquid comprising the coating material with the gas, divided by the radius of the stable unified jet. Details relating to the technology are described within issued U.S. Patent 6,234,402 issued May 22, 2001 and incorporated herein by reference. Those skilled in the art will understand that some adjustments may be made in the density and velocity of the different fluids and gases used in order to obtain the desired result in terms of the fluid - fluid interfaces including the particle interface between the coating material and the inner liquid material as well as the stable interface between the gas and the coating material. It is desirable to obtain the stable microjet stream which has substantially no aberrations or perturbations in the stream

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making it possible for the stream to disassociate into very uniform size and shaped particles. The two related systems shown in Figure 2 and 3 make it possible to maintain a stable liquid-gas interface between the outer surface of the liquid or coating material and the gas thereby forming a stable jet which is focused on the exit orifice of the pressure chamber resulting in particles which have very small deviation in terms of diameter from one particle to the next. It is also possible to create hollow particles and to reverse the positioning of the different fluids. For examples, the center tube can be used to supply gas whereas the pressure chamber can be used to supply a liquid. The technology for such is described within issued U.S. Patent 6,196,525 issued March 6, 2001 which patent along with other patents cited herein is incorporated in its entirety.

DISSOLUTION PROFILES

[00218] When any particle dissolves in any solvent the amount of solute in the solution increases over time. However, some solvents are present in systems where the portion of the dissolving solute is being removed from the solution. This could take place in a chemical reaction where a portion of the dissolved solute reacts with another components present in the system. However, the most typical situation is where a drug present in an area and diffuses away from that area which subtracts solute drug from the surrounding area. In any such system the dissolution profile over time shows an increase followed by a steady state followed by a decrease as is shown by the solid line in Figure 4. It is desirable to maintain the level of a drug above the therapeutic level shown by the line of short dashes but below a toxic level shown by the line of long dashes or level where addition drug provides no additional benefit. Maintaining the level of drug in a desired range for a significant period is difficult to obtain particularly when using a single type of particle.

[00219] Figure 5 shows how the therapeutic level can be maintained over a longer period of time using two different types of particles. In Figure 5 the independent effect of a first type of particle is shown by the solid line. The dashed curve shows the independent effect of a second type of coated particle. The dotted curve shows the combined effect of the two types of particles. When the particle of the first type are

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completely dissolved and are being metabolized out of the system the coatings on the particle of the second type have dissolved and the rate of dissolution matches the rate at which all drug in the system is being diffused out of the desired area. Thus, a longer steady state period is maintained. This effect is further enhanced using three different types of particles as shown in Figure 6.

[00220] Controlled release within the scope of this invention can be taken to mean any one of a number of extended release dosage forms. The following terms may be considered to be substantially equivalent to controlled release, for the purposes of the present invention: continuous release, controlled release, delayed release, depot, gradual release, long-term release, programmed release, prolonged release, proportionate release, protracted release, repository, retard, slow release, spaced release, sustained release, time coat, timed release, delayed action, extended action, layered-time action, long acting, prolonged action, repeated action, slowing acting, sustained action, sustained-action medications, and extended release. Further discussions of these terms may be found in Lesczek Krowczynski, Extended-Release Dosage Forms, 1987 (CRC Press, Inc.).

[00221] There are corporations with specific expertise in drug delivery technologies including controlled release oral formulations such as Alza corporation and Elan. A search of patents, published patent applications and related publications will provide those skilled in the art reading this disclosure with significant possible controlled release technologies. Examples include the technologies disclosed in any of the U.S. patents 5,637,320 issued June 10, 1997; 5,505,962 issued April 9, 1996; 5,641,745 issued June 24, 1997; and 5,641,515 issued June 24, 1997. Although specific technologies are disclosed here and in these patents the invention is more general than any specific technology. This includes the discovery that by placing pharmaceutically active drug in a plurality of controlled release particle groups which maintain therapeutic levels (but not toxic levels) over periods of time which are longer as compared to quick release formulations, but shorter compared to bone cement, improved unexpected results are obtained.

PARTICLES FORMED USING SUPERCRITICAL FLUID PRECIPITATION

[00222] The devices, systems and methodology disclosed and described above in connection with Figures 2 and 3 can also be used in combination with supercritical fluid precipitation technology of the type described within U.S. Patent 6,063,910 issued May 16, 2000; 5,766,637 issued June 16, 1998; 6,228,394 issued May 8, 2001; and 6,095,134 issued August 1, 2000 all of which are incorporated herein by reference in their entirety. Basically, the technology utilizes a supercritical fluid such as liquid CO₂ in order to form solid particles of a material such as a drug or a protein for use in a formulation.

[00223] Referring to Figure 2 the gas source 27 could be replaced with a liquid CO₂ and the liquid CO₂ could become the focusing fluid. The liquid 23 supplied into the tube 21 could be any liquid comprised of any desired material. However, the liquid 23 would preferably be a liquid which included an active compound such as a drug which is dissolved within a solvent such as water and further combined with a solvent such as ethanol. The solvent liquid 23 is focused by the surrounding liquid 26 which may be CO₂. When the CO₂ exits the pressure chamber 28 via the orifice opening 29 the rapid evaporation draws the liquid water and ethanol away leaving dry particles 31.

[00224] Referring to Figure 3 it would also be possible to use supercritical fluids in place of the coating 52 or in place of the gas 51. Those skilled in the art will recognize that a variety of different combinations of liquids, gases, solutions and supercritical fluids are possible using the systems as shown and described above with respect to Figures 2 and 3 particularly when taken in combination with the above-referenced patents which disclose basic technology used in the field of supercritical fluid precipitation.

HETEROGENOUS PARTICLE FORMULATIONS

[00225] A packet of formulation can be a disposable container of spheres with a group or plurality of groups of spheres in each packet. The packet may be a syringe which includes the particles in a liquid or a gel such as FlorsealTM. Alternatively, the packet may be a sealed container such as a foil packet holding an absorbable collagen sponge

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having the particles dispersed evenly therein. A first group of spherical particles is present wherein each particle of the first group has a same diameter as other particles in the group with a margin of error in terms of particle diameter size of approximately $\pm 10\%$ or less. The formulation may then include a second group of spherical particles wherein each particle of the second group has the same diameter as the other particles in the second group with a margin of error of about $\pm 10\%$ or less. The particles within the first group are different from the particles within the second group (e.g. see Table 1) and preferably have a difference in terms of the steady state levels which difference is sufficient to provide a longer steady state level of a reverse transcriptase inhibitor to the vagina than either of the groups by themselves. Preferably, the first group of particles and the second group of particles each comprise 100 or more particles, more preferably a 1,000 of more particles, and still more preferably 10,000 or more particles and may comprise 10^5 to 10^{10} or more particles.

[00226] Although the heterogeneous groups of particles in a formulation can be produced using particle formation technology of various types the technology as described above with respect to Figure 2 and 3 are preferred in that they produce very uniform sized and shaped particles. Further, the particles may be solid spheres which may be produced using the technology as shown in Figure 2. A formulation or device of the invention may include groups of particles wherein the particles are coated using the technology as shown within Figure 3. A formulation may include 3 or more groups of spherical particles wherein the particles within each group are the same relative to other particles in that group and are different between the groups. A formulation may comprise at least some particles which are not coated e.g. a first group of particles with no coating and a relatively small particle size. Thus, the first group of particles will provide for substantially immediate dissolution and release of all of the compound or drug which is present in the particles. This causes the drug to quickly reach a therapeutic level in the desired surrounding area. The remaining groups of particles are larger and include polymers and remain undissolved. When a known amount of time has passed diffusion will have removed from the surrounding area (e.g. the bone) a sufficient amount of the drug added by the first group such that the concentration of the

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drug in the surrounding area is beginning to decline. With this decline the second group of particles increase their dissolution to add drug to the surrounding area thereby gradually increasing the concentration via the second group of particles at a rate substantially corresponding to the rate at which drug from the first group of particles is being decreased and diffused out of the area. This is shown within the graph of Figure 5. The process can be repeated several times with several different groups of particles and three different groups of particles are shown within the graph of Figure 6. The groups may be included in a packet of formulation which may be a disposable, one use, syringe with a gel and the syringe, gel, and particles may be included in a kit. The kit may include another drug which compliments the drug in the particles.

[00227] In one embodiment of the invention a reverse transcriptase inhibitor is dissolved in a solvent which may be water, ethanol or a combination of water and ethanol. The solution is saturated with drug and the saturated solution is then coated with a polymer material which can be quickly cured by the addition of energy or evaporation as shown within Figure 3. Thus, a group of particles is formed wherein the particles are comprised of a liquid center which liquid is comprised of a saturated solution of drug and solvent in an outer core of polymer material which is substantially inert i.e. does not provide a pharmacological effect. Such particles are produced in a variety of different size ranges. Each size is used to produce a group of particles which, by itself, is sufficient to provide for therapeutic levels of a drug to a given area such as an area surrounding the implant. When the coating dissolves the liquid within the spheres, which is a liquid drug (e.g. a drug in an aqueous solution) is immediately released. When the drug has diffused away to the point of beginning to drop below therapeutic levels the next group of particles with a thicker coating have dissolved to the point where the drug within these particles is released raising the level of drug in the surrounding area. By including a plurality of different groups it is possible to maintain the therapeutic level of the drug over a long period of time e.g. 1 day, several days (2 to 6 days) or 72 hours $\pm$ 12 hours. Care should be taken to avoid developing resistant bacteria.

[00228] Those skilled in the art will recognize that variability in terms of the rate at which the polymer material dissolves can be changed by changing the composition of the polymer material as some materials will dissolve more quickly than others. Accordingly, the different groups of particles within the formulation may be particles which are all of the same size, but have different polymer materials. In one embodiment the composition of coating on one group of particles dissolves more rapidly than the coating composition on another group within the formulation.

EXAMPLES

[00229] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

EXAMPLE 1

[00230] Those skilled in the art will recognize that the technology described here can be provided to a number of different types of drugs and to heterogenous formulations of all different numbers of particle groups. However, here a specific example is described wherein the active drug is first included within particles which have no coating and thereafter are included within two additional groups of particles wherein the percent thickness of the spheres is varied.

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Capsule Thickness	Sphere Diameter		
	5 microns	10 microns	20 microns
0	S/V = 2.4	S/V = 1.2	S/V = 0.6
10%	S/V = 4.7	S/V = 2.3	S/V = 1.2
30%	S/V = 38	S/V = 19	S/V = 9.4

[00231] The surface area to volume ratio numbers in Table 6 must be taken in the context of the capsule thickness. Microspheres with a capsule thickness of zero are composed entirely of active drug; there is by definition no inactive ingredient forming a capsule layer. Therefore, even though a 10 μ m microsphere with zero capsule thickness has the same surface area to volume ratio (1.2) as a 20 μ m microsphere with a 10% capsule thickness, release of active drug from the 20 μ m sphere will occur only after the outer layer has dissolved whereas active drug from the 10 μ m sphere in this example will begin to be released as soon as microsphere dissolution begins.

[00232] In addition, in the context of this invention, high surface area to volume values do not necessarily mean faster release of active drug into the area surrounding the implant. This is because, for the case of non-zero capsule thickness microspheres, the outer material is an inactive ingredient.

[00233] By having a formulation in which a distinct capsule thickness is present in microspheres of a distinct size, a true programmable controlled release profile can be engineered by selecting (a) the capsule thickness and microsphere size and (b) by selecting in which proportions different populations of microspheres selected in (a) are combined and bound to the implant (e.g. screw) or other device.

[00234] For example, a slow release tenofovir formulation bound to indentations on a screw could consist of 1/3 zero capsule thickness 5 μ m microspheres for rapid release, 1/3 10% capsule thickness 10 μ m spheres for intermediate release and 1/3 10% capsule thickness 20 μ m microspheres for long term release as part of a single formulation. Because the capsule of inactive material must be largely dissolved before active drug release, this approach has the distinct advantage of minimizing the overlap of delivery by the various formulation components. This allows the aggregate PK

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profile of the formulation to be formed by superposition of the release profiles of the components of the formulation.

[00235] The preceding merely illustrates the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and embodiments of the invention as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof. Additionally, it is intended that such equivalents include both currently known equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function, regardless of structure. The scope of the present invention, therefore, is not intended to be limited to the exemplary embodiments shown and described herein. Rather, the scope and spirit of present invention is embodied by the appended claims.

CLAIMS

That which is claimed is:

1. A formulation, comprising:
a plurality of particles comprised of a reverse transcriptase inhibitor and a biocompatible polymer; and
a pharmaceutically acceptable gel carrier having the particles dispersed therein.
2. The formulation of claim 1, wherein:
the biocompatible polymer is comprised of polylactic glycolic acid (PLGA);
and
wherein the reverse transcriptase inhibitor is present in an amount in the range of 100 mg to 600 mg and wherein the reverse transcriptase inhibitor is selected from the group consisting of Zidovudine, Didanosine, Zalcitabine, Stavudine, Lamivudine, Abacavir, Emtricitabine, Entecavir, Apricitabine, Tenofovir, Adefovir, Efavirenz, Nevirapine, Delavirdine, Etravirine.
3. The formulation of any of claims 1 and 2, further comprising:
a flavoring agent in the gel; and
a compound which generates heat via an exothermic reaction.
4. The formulation of any of claims 1 to 3, wherein comprising:
flavoring agent having a flavor selected from the group consisting of lemon, mint, cherry, strawberry, bubble gum, pina colada and chocolate; and
a compound which generates heat which compound is selected from the group consisting of propylene glycol, polyethylene glycol, hydroxypropyl cellulose, and lactic acid, and wherein the reverse transcriptase inhibitor is tenofovir and is present in an amount of 300 mg $\pm$ 10%.

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5. The formulation of any of claims 1 to 4, wherein the particles comprise:
 - a first group of spherical particles comprising 100 or more particles wherein each particle of the first group has the same diameter as other particles in the first group with a margin of error of $\pm 10\%$ or less;
 - a second group of spherical particles comprising 100 or more particles wherein each particle of the second group has the same diameter as other particles in the second group with a margin of error of $\pm 10\%$ or less;
 - wherein particles of the first group dissolve at a rate which is faster than a rate at which the particles of the second group dissolve and the formulation provides therapeutic levels of tenofovir to a target area.
6. The formulation of any of claims 1 to 5, wherein the particles further comprise:
 - a third group of spherical particles comprising 100 or more particles wherein each particle of the third group has the same diameter as other particles in the third group with a margin of error of $\pm 10\%$ or less;
 - wherein particles of the third group dissolve at a rate different from a rate at which the particles of the first and second groups dissolve.
7. The formulation of any of claims 1 to 6, wherein the particles of each group dissolve at a rate per unit of time which is different from a rate of dissolution of any other of the groups of particles by an amount of about 25% or more.
8. The formulation of any of claims 1 to 7, wherein the spherical particles in each group have a diameter in a range of from about 40 micrometers to about 2 micrometers or a diameter in a range of from about 30 micrometers to about 4 micrometers.
9. Use of any of the formulations of claims 1-8 in improving patient compliance with controlled release tenofovir.

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10. A drug formulation capsule, comprising:
a polymeric biocompatible capsule; and
a group of particles comprised of a reverse transcriptase inhibitor and a pharmaceutically acceptable carrier; and
a second group of particles comprised of a reverse transcriptase inhibitor and a pharmaceutically acceptable carrier;
wherein the particles within the first group of particles are substantially identical to each other and particles within the second group of particles are substantially identical to each other and different from particles in the first group, wherein the first group of particles provides for immediate release of the reverse transcriptase inhibitor and the second group of particles provides for controlled release of the reverse transcriptase inhibitor over a period of time from 24 hours to 7 days.

11. A drug formulation capsule of any of claims 1 to 10, wherein:
the reverse transcriptase inhibitor is present in an amount in the range of 100 mg to 600 mg and wherein the reverse transcriptase inhibitor is selected from the group consisting of Zidovudine, Didanosine, Zalcitabine, Stavudine, Lamivudine, Abacavir, Emtricitabine, Entecavir, Apricitabine, Tenofovir, Adefovir, Efavirenz, Nevirapine, Delavirdine, Etravirine;

wherein the flavoring agent is a flavor selected from the group consisting of lemon, mint, cherry, strawberry, bubble gum, pina colada and chocolate; and

wherein the compound which generates heat is selected from the group consisting of propylene glycol, polyethylene glycol, hydroxypropyl cellulose, and lactic acid, and wherein the reverse transcriptase inhibitor is tenofovir and is present in an amount of 300 mg $\pm$ 10%.

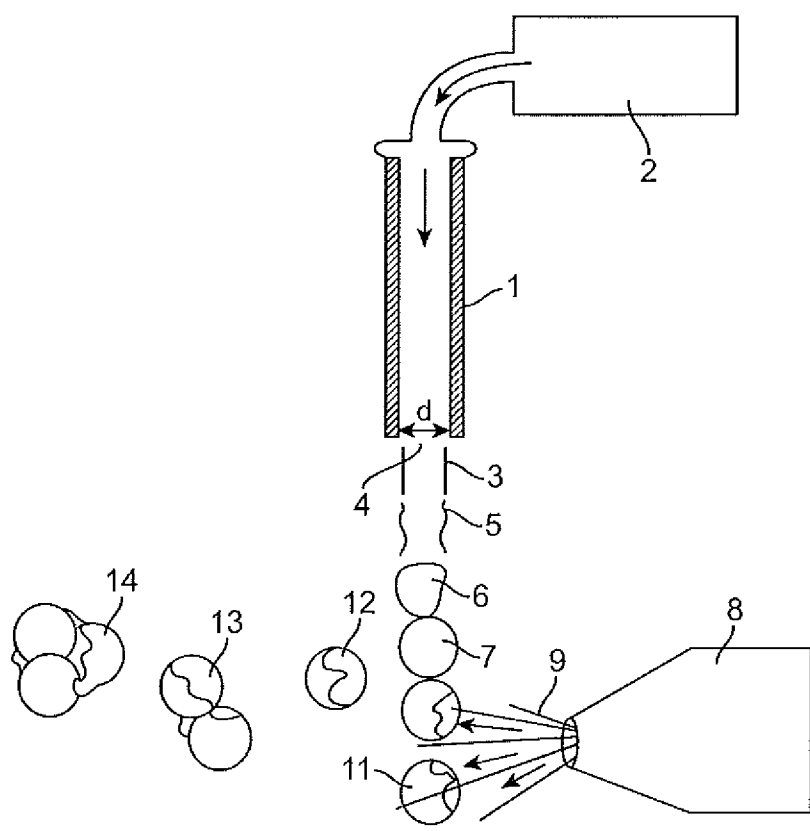


FIG. 1

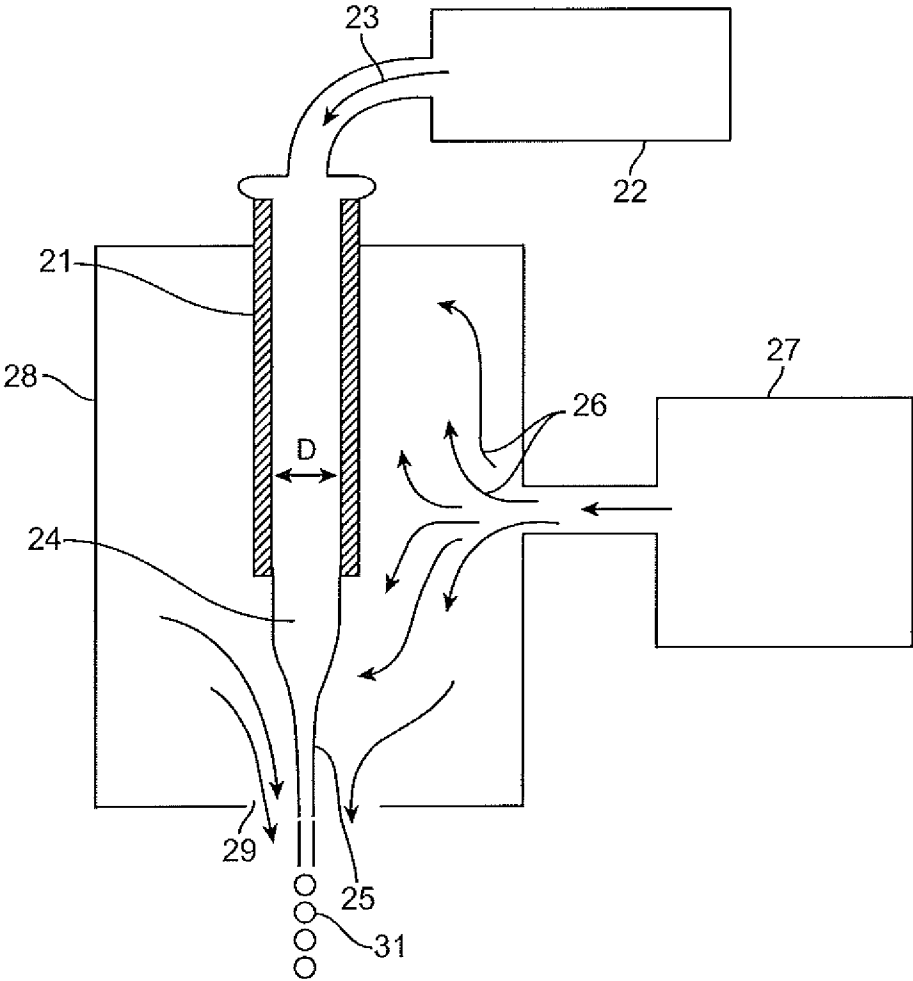


FIG. 2

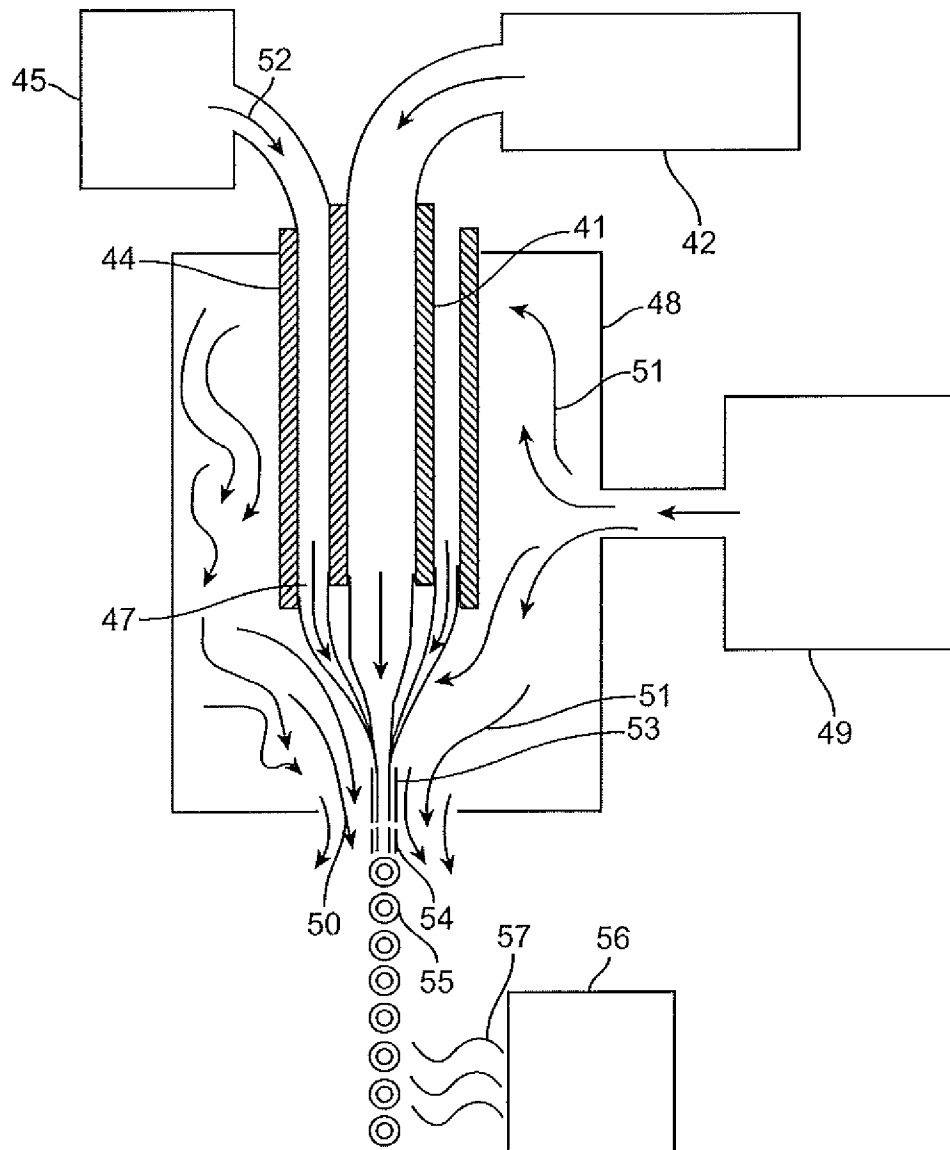


FIG. 3

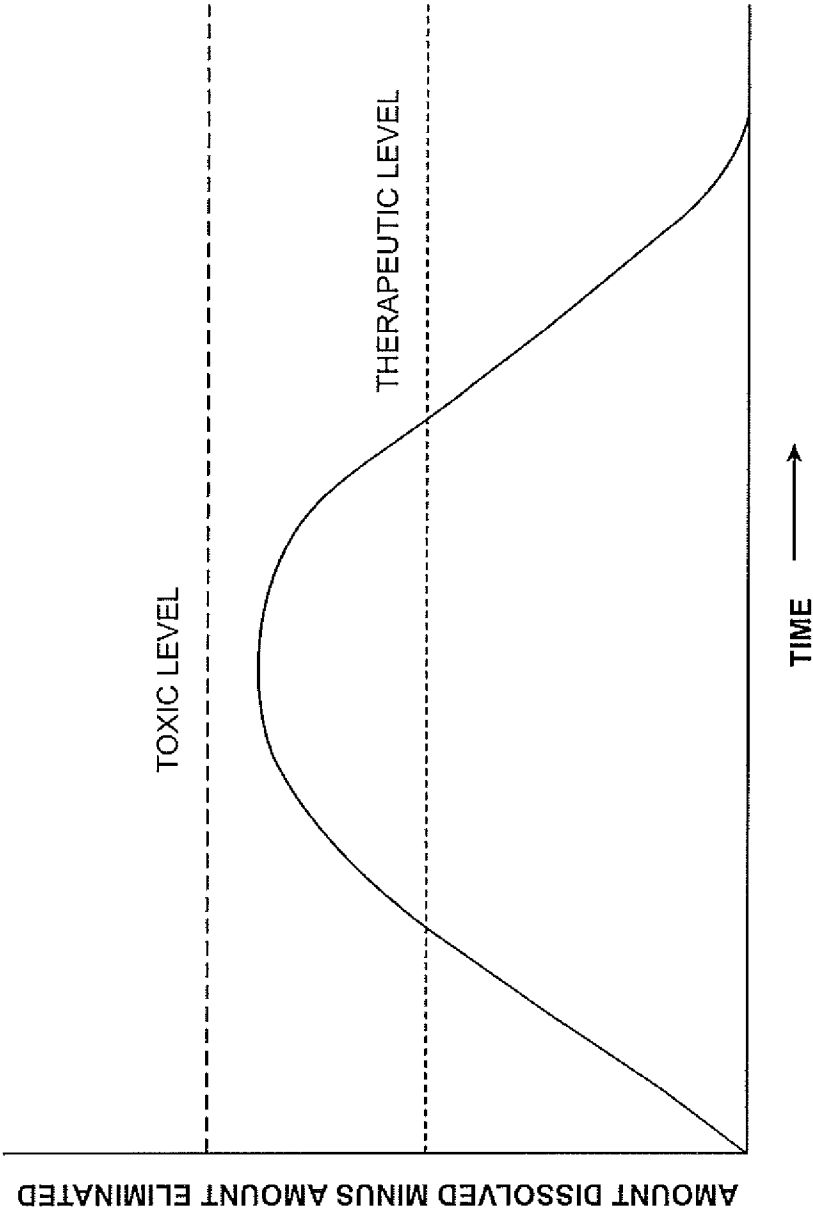


FIG. 4

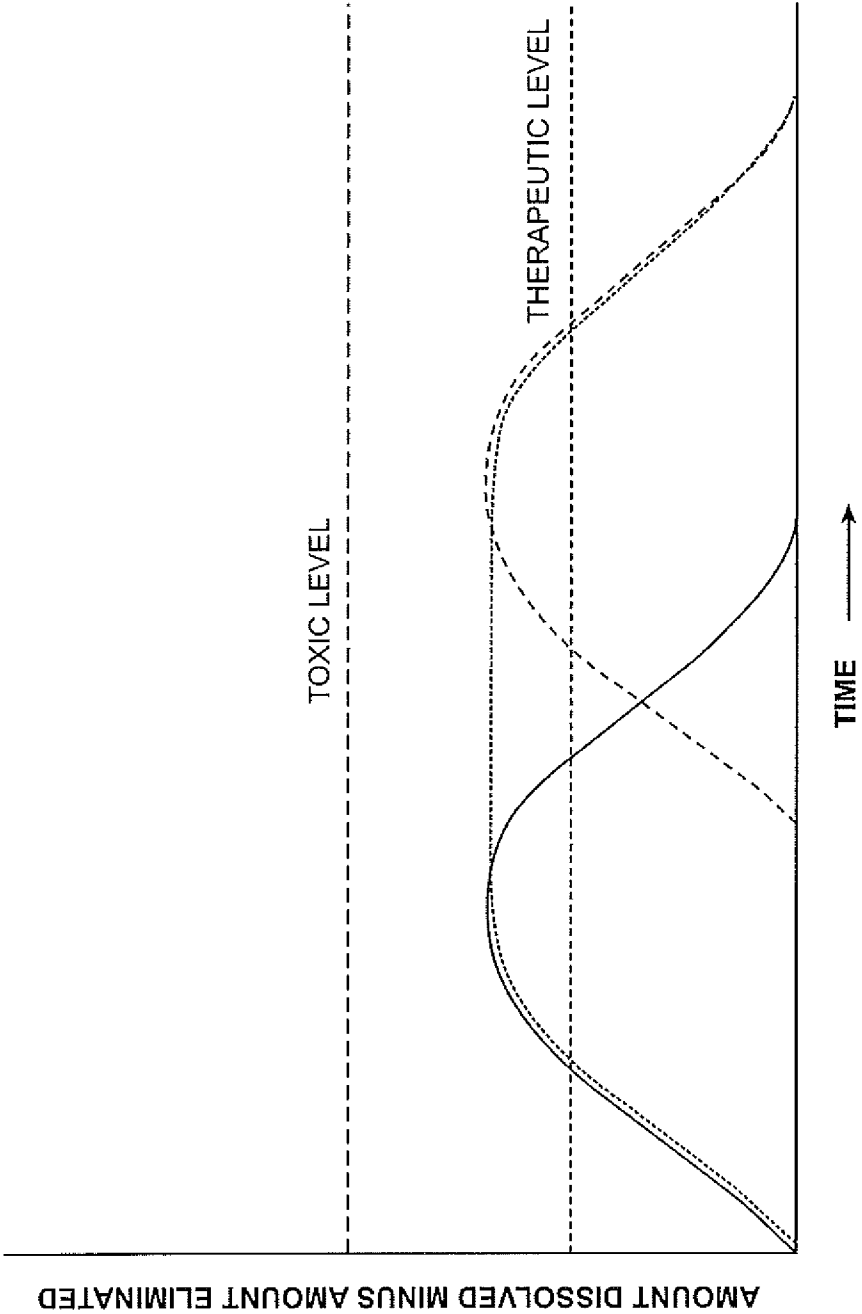


FIG. 5

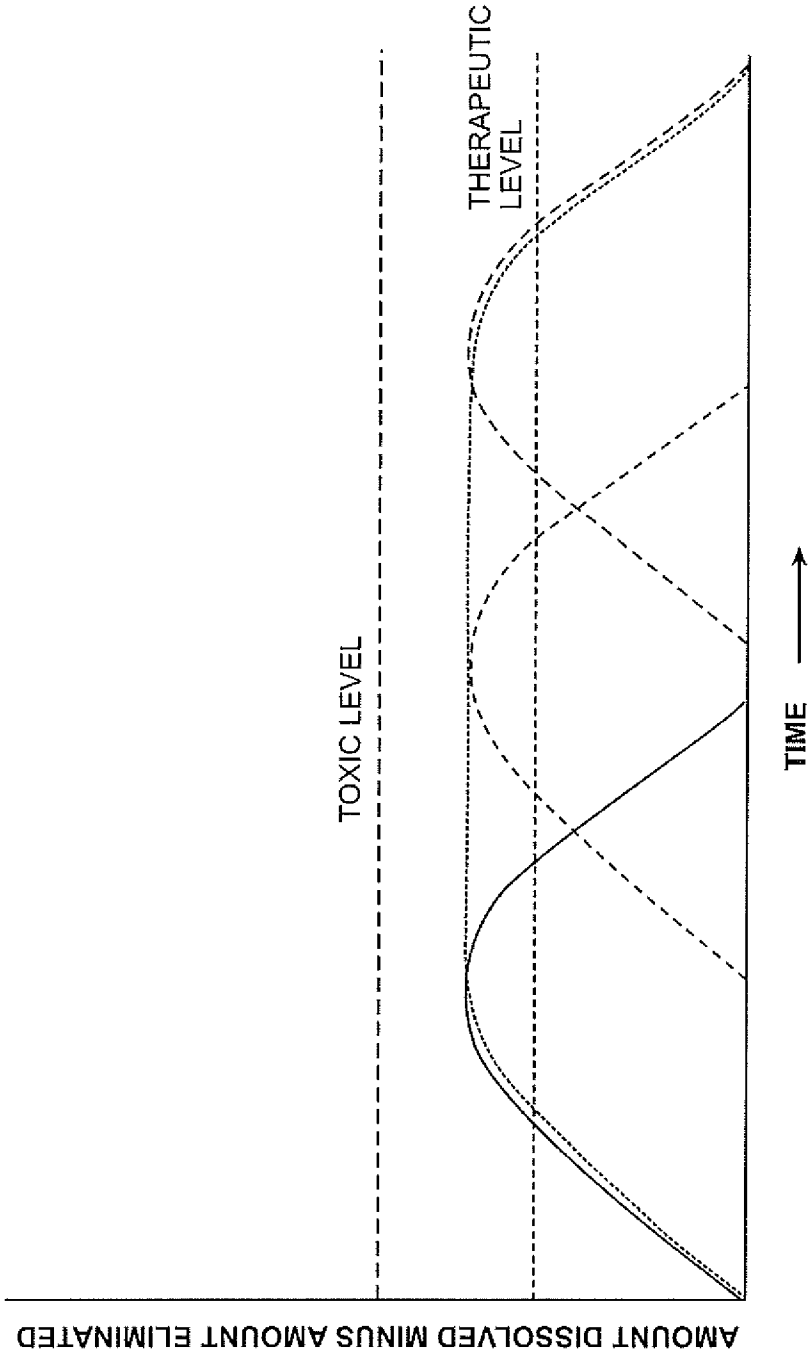
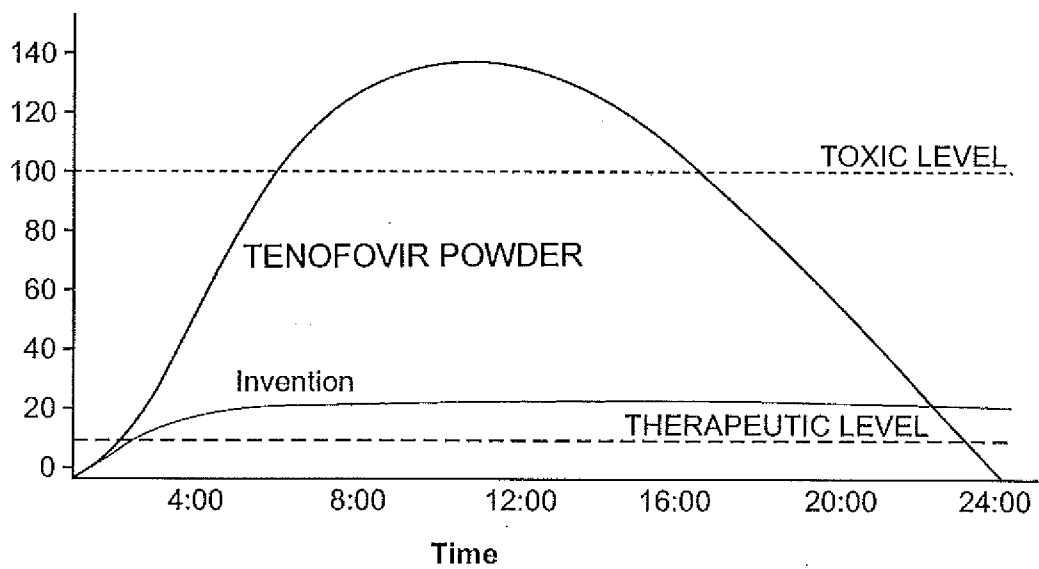


FIG. 6

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IN-VIVO FLOSEAL® TENOFOVIR RELEASE INTO VAGINA**FIG. 7**

INTERNATIONAL SEARCH REPORT

international application no.

PCT/US 14/22338

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61F 6/06 (2014.01)

USPC - 424/434, 430

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC -424/434, 430Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
(see search terms below)Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, PubWest, ProQuest Dialog
Search Terms: reverse transcriptase, inhibitor, Zidovudine, Didanosine, Zalcitabine, Stavudine, Lamivudine, Abacavir, Efavirenz, Nevirapine, Delavirdine, Etravirine, polymer, polylactic glycolic, PLGA, particle, biocompatible, capsule, formulation, disperse, group

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/0291220 A1 (Rubsamen) 18 November 2010 (18.11.2010) para [0010], [0081], [0160]	1-2 and 10
Y	WO 2013/013172 A1 (Shelke et.) 24 January 2013 (24.01.2013) para [0021], [0030], [0034]-[0035]	1-2 and 10
A	US 2011/0045076 A1 (Kiser et al.) 24 February 2011 (24.02.2011) para [0034]-[0035]	1-2 and 10

☐ Further documents are listed in the continuation of Box C.


* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

02 June 2014 (02.06.2014)

Date of mailing of the international search report

24 JUN 2014

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

international application no.

PCT/US 14/22338

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 3-9 and 11
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.