well suited for reformulation as long-acting injectable products. In large part, this is due to suboptimal physicochemical properties limiting their formulation as conventional drug suspensions, as well as insufficient antiviral potency resulting in high monthly dosing requirements. Even for cabotegravir or rilpivirine, two drugs being studied as long-acting injectible formulations, large injection volumes and multiple injections are required to achieve pharmacokinetic profiles supportive of monthly dosing. See, e.g., Spreen, W. R., et al., Long-acting injectable antiretrovirals for HIV treatment and prevention. *Current Opinion in Hiv and Aids* **2013,** 8, (6), 565-571; Rajoli, R. K. R., et al., Physiologically Based Pharmacokinetic Modelling to Inform Development of Intramuscular Long-Acting Nanoformulations for HIV. *Clinical Pharmacokinetics* **2015,** 54, (6), 639-650; Baert, L., et al., Development of a long-acting injectable formulation with nanoparticles of rilpivirine (TMC278) for HIV treatment. *European Journal of Pharmaceutics and Biopharmaceutics* **2009,** 72, (3), 502-508; Van 't Klooster, G., et al., Pharmacokinetics and Disposition of Rilpivirine (TMC278) Nanosuspension as a Long-Acting Injectable Antiretroviral Formulation. *Antimicrobial Agents and Chemotherapy* **2010,** 54, (5), 2042-2050. Thus, novel formulation approaches capable of delivering extended-duration pharmacokinetic characteristics for molecules of diverse physicochemical properties at practical injection volumes and with a limited number of injections are highly desirable.

SUMMARY ~~OF THE INVENTION~~

This ~~invention~~ disclosure relates to novel implant drug delivery systems for long-acting delivery of antiviral drugs. These compositions are useful for the treatment or prevention of human immunodeficiency virus (HIV) infection.

In one aspect, the present disclosure relates to an implant drug delivery system comprising: (a) a core comprising a biocompatible nonerodible polymer and 4'-ethynyl-2-fluoro-2'-deoxyadenosine anhydrate, which is present in the core between 1% to 60% by weight, and (b) a biocompatible nonerodible diffusional barrier comprising a polymer, wherein said diffusional barrier has a thickness between 50 µm and 300 µm, wherein said implant drug delivery system is for subdermal implantation and 4'-ethynyl-2-fluoro-2'-deoxyadenosine anhydrate is capable of continual release in vivo at a rate resulting in a plasma concentration of 4'-ethynyl-2-fluoro-2'-deoxyadenosine between 0.02 ng/mL and 300.0 ng/mL for a period of six months to thirty-six months.

In another aspect, the present disclosure relates to an implant drug delivery system comprising: (a) a core comprising a biocompatible nonerodible polymer and 4'-ethynyl-

2-fluoro-2'-deoxyadenosine anhydrate, which is present in the core between 1% to 60% by weight, and (b) a biocompatible nonerodible diffusional barrier comprising a polymer, wherein said diffusional barrier has a thickness between 50 µm and 300 µm, wherein said 4'-ethynyl-2-fluoro-2'-deoxyadenosine anhydrate has an in vitro release rate of 0.03 to 0.07 mg/day when measured between one and six months.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 is a graph of a Powder X-Ray Diffraction ("PXRD") pattern of anhydrate crystalline Form 4 of EFdA, generated using the equipment and methods described herein. The graph plots the intensity of the peaks as defined by counts per second versus the diffraction angle 2 theta (2Θ) in degrees.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to novel implant drug delivery systems for long-acting delivery of antiviral drugs. The novel implant drug delivery systems comprise a polymer and an antiviral agent. These implant drug delivery systems are useful for the treatment or prevention

WHAT IS CLAIMED IS:

1. An implant drug delivery system comprising:

(a) a core comprising a biocompatible nonerodible polymer and 4'-ethynyl-2-fluoro-2'-deoxyadenosine anhydrate, which is present in the core between 1% to 60% by weight, and

(b) a biocompatible nonerodible diffusional barrier comprising a polymer, wherein said diffusional barrier has a thickness between 50 µm and 300 µm,

wherein said implant drug delivery system is ~~implanted subdermally~~for subdermal implantation and 4'-ethynyl-2-fluoro-2'-deoxyadenosine anhydrate is ~~continually~~ capable of continual release~~d~~ *in vivo* at a rate resulting in a plasma concentration of 4'-ethynyl-2-fluoro-2'-deoxyadenosine between 0.02 ng/mL and 300.0 ng/mL for a period of six months to thirty-six months.

2. The implant drug delivery system of Claim 1 wherein the 4'-ethynyl-2-fluoro-2'-deoxyadenosine plasma concentration is between 0.02 ng/mL and 30.0 ng/mL.

3. The implant drug delivery system of Claim 2 wherein the 4'-ethynyl-2-fluoro-2'-deoxyadenosine plasma concentration is between 0.02 ng/mL and 8.0 ng/mL.

4. The implant drug delivery system of Claim 1 wherein the 4'-ethynyl-2-fluoro-2'-deoxyadenosine anhydrate is present in the core between 10% to 60% by weight.

5. The implant drug delivery system of Claim 4 wherein the 4'-ethynyl-2-fluoro-2'-deoxyadenosine anhydrate is present in the core at 15% to 40% by weight.

6. The implant drug delivery system of Claim 4 wherein the 4'-ethynyl-2-fluoro-2'-deoxyadenosine anhydrate is present in the core at about 40% by weight.

7. The implant drug delivery system of Claim 4 wherein the 4'-ethynyl-2-fluoro-2'-deoxyadenosine anhydrate is present in the core at about 60% by weight.

8. The implant drug delivery system of Claim 1 wherein the biocompatible nonerodible polymer in the core is selected from the group consisting of ethylene vinylacetate copolymer (EVA), poly(urethane), silicone, crosslinked poly(vinyl alcohol), poly(hydroxy ethylmethacrylate), acyl substituted cellulose acetates, partially hydrolyzed alkylene-vinyl acetate copolymers, completely hydrolyzed alkylene-vinyl acetate copolymers, unplasticized polyvinyl chloride, crosslinked homopolymers of polyvinyl acetate, crosslinked copolymers of polyvinyl acetate, crosslinked polyesters of acrylic acid, crosslinked polyesters of methacrylic acid, polyvinyl alkyl ethers, polyvinyl fluoride, polycarbonate, polyamide, polysulphones, styrene acrylonitrile copolymers, crosslinked poly(ethylene oxide), poly(alkylenes), poly(vinyl imidazole), poly(esters), poly(ethylene terephthalate), polyphosphazenes, chlorosulphonated polylefins, and combinations thereof.

9. The implant drug delivery system of Claim 8 wherein the biocompatible nonerodible polymer is poly(urethane).

10. The implant drug delivery system of Claim 1, wherein the diffusional barrier comprises a hydrophilic polymer or a hydrophobic polymer with a soluble filler.

11. The implant drug delivery system of Claim 10, wherein the diffusional barrier comprises a polymer selected from the group consisting of ethylene vinylacetate copolymer (EVA), silicone, crosslinked poly(vinyl alcohol), unplasticized polyvinyl chloride, crosslinked homopolymers of polyvinyl acetate, crosslinked copolymers of polyvinyl acetate, crosslinked polyesters of acrylic acid, crosslinked polyesters of methacrylic acid, polyvinyl alkyl ethers, polyvinyl fluoride, polycarbonate, polyamide, polysulphones, styrene acrylonitrile copolymers, crosslinked poly(ethylene oxide), poly(alkylenes), poly(vinyl imidazole), poly(ethylene terephthalate), poly(urethane), poly(hydroxy ethylmethacrylate), acyl substituted cellulose acetates, partially hydrolyzed alkylene-vinyl acetate copolymers, completely hydrolyzed alkylene-vinyl acetate copolymers, poly(esters), polyphosphazenes, chlorosulphonated polylefins, and combinations thereof.

12. The implant drug delivery system of Claim 11, wherein the diffusional barrier comprises a polymer selected from the group consisting of poly(urethane), poly(hydroxy ethylmethacrylate), acyl substituted cellulose acetates, partially hydrolyzed alkylene-vinyl

acetate copolymers, completely hydrolyzed alkylene-vinyl acetate copolymers, poly(esters), polyphosphazenes, chlorosulphonated polylefins, and combinations thereof.

13. The implant drug delivery system of Claim 10, wherein the diffusional barrier comprises poly(urethane).

14. The implant drug delivery system of Claim 11, wherein the poly(urethane) has a water uptake of between 1% and 20% by weight.

15. The implant drug delivery system of Claim 1 wherein the diffusional barrier has a thickness between 50 μm and 200 μm.

16. The implant drug delivery system of Claim 1 wherein the core and the biocompatible nonerodible diffusional barrier both compirse poly(urethane).

17. The implant drug delivery system of Claim 1, wherein the core and the biocompatible nonerodible diffusional barrier are prepared by co-extrusion, and the co-extrusion is carried out at a temperature between 130°C and 190°C.

18. The implant drug delivery system of Claim 17 wherein the co-extrusion is carried out at a temperature between 130°C and 160°C.

19. The implant drug delivery system of Claim 1 wherein the 4'-ethynyl-2-fluoro-2'-deoxyadenosine anhydrate is characterized by a powder x-ray diffraction pattern with at least peaks at diffraction angles degrees 2 theta (+/- 0.2°) 11.79, 12.39, 14.70 and 15.51 in a powder x-ray diffraction obtained using Cu K alpha radiation.

20. The implant drug delivery system of Claim 1 comprising between 1% and 20% by weight of a radiopaque material.

21. The implant drug delivery system of Claim 20 wherein the radiopaque material is barium sulfate.

22. The implant drug delivery system of Claim 1 wherein the 4'-ethynyl-2-fluoro-2'-deoxyadenosine is released at therapeutic concentrations for a duration from between twenty-four months and thirty-six months.

~~23. A method of treating or preventing HIV infection with an implant drug delivery system according to Claim 1.~~

~~24.~~23. An implant drug delivery system comprising:

(a) a core comprising a biocompatible nonerodible polymer and 4'-ethynyl-2-fluoro-2'-deoxyadenosine anhydrate, which is present in the core between 1% to 60% by weight, and

(b) a biocompatible nonerodible diffusional barrier comprising a polymer, wherein said diffusional barrier has a thickness between 50 µm and 300 µm,

wherein said 4'-ethynyl-2-fluoro-2'-deoxyadenosine anhydrate has an *in vitro* release rate of 0.03 to 0.07 mg/day when measured between one and six months.

~~25.~~24. The implant drug delivery system of Claim ~~24~~ 23 wherein 4'-ethynyl-2-fluoro-2'-deoxyadenosine anhydrate has an *in vitro* release rate of 0.07 mg/day when measured at day 30.

~~26.~~25. The implant drug delivery system of Claim ~~24~~ 23 wherein 4'-ethynyl-2-fluoro-2'-deoxyadenosine anhydrate has an *in vitro* release rate of 0.04 mg/day when measured at day 60.

~~27.~~26. The implant drug delivery system of Claim ~~24~~ 23 wherein 4'-ethynyl-2-fluoro-2'-deoxyadenosine anhydrate has an *in vitro* release rate of 0.03 mg/day when measured at six months.