PHARMACEUTICAL FORMULATIONS OF CYCLOSPORINE ANALOGS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Patent Application Number 62/771,453, filed on November 26, 2018, the content of which is incorporated herein by reference herein in its entirety.

FIELD OF THE DISCLOSURE

[0002] The present disclosure is directed to pharmaceutical compositions (e.g., self-microemulsifying drug delivery systems "SMEDDS") of cyclosporine A analogs (e.g., CRV431, a non-immunosuppressive analogue of cyclosporine A). In some embodiments, the SMEDDS are stable, can readily solubilize the CRV431, and can enable a high bodily exposure of CRV431.

BACKGROUND OF THE DISCLOSURE

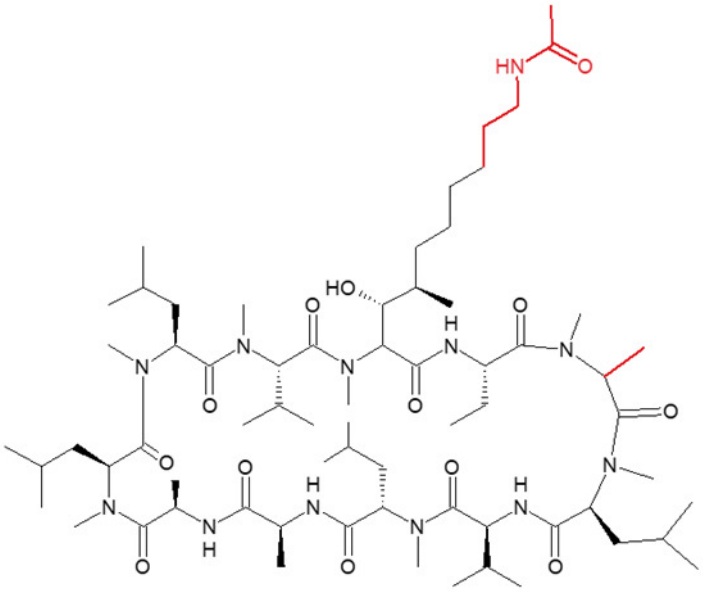
[0003] CRV431 is a small molecule cyclophilin inhibitor under clinical development for the treatment of liver diseases including liver fibrosis and hepatocellular carcinoma. In preclinical studies CRV431 has shown anti-viral activity against a number of viruses including hepatitis B, hepatitis C, and HIV and anti-fibrotic activity in the liver in a number of *in vivo* models. CRV431 (shown in FIG. 1B) is a derivative of cyclosporine A (CsA) (shown in FIG. 1A), a neutral cyclic peptide consisting of eleven amino acids, wherein amino acids 1 and 3 have been chemically modified as shown in FIG. 1B.

SUMMARY

[0004] The present disclosure provides a stable SMEDDS formulation of CRV431 that enables good solubility of a derivative of cyclosporine A (e.g., CRV431) and enables significant blood exposure in humans following a single oral dose in healthy subjects.

[0004a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising:

(a) CRV431 at a concentration of from 10 mg/mL to 90 mg/mL:



(CRV431);

(b) Vitamin E;

(c) glyceryl monolinoleate;

(d) propylene glycol;

(e) diethylene glycol monoethyl ether;

(f) ethanol; and

(g) polyoxyl castor oil, wherein Vitamin E, glyceryl monolinoleate, propylene glycol, diethylene glycol monoethyl ether, ethanol, and polyoxyl castor oil are at a weight ratio, respectively, of 1/1.5/2.5/5/2.4/5.

[0004b] In another aspect, the present disclosure refers to the pharmaceutical composition as described herein for use as a medicament.

[0004c] In another aspect, the present disclosure refers to a use of a pharmaceutical composition as described herein in the manufacture of a medicament.

[0004d] In yet another aspect, the present disclosure refers to the pharmaceutical composition as described herein for use in the treatment or prevention of a disease in a subject, wherein the disease is liver disease.

[0004e] In yet another aspect, the present disclosure refers to a use of a pharmaceutical composition as described herein in the manufacture of a medicament for the treatment or prevention of a disease in a subject, wherein the disease is liver disease.

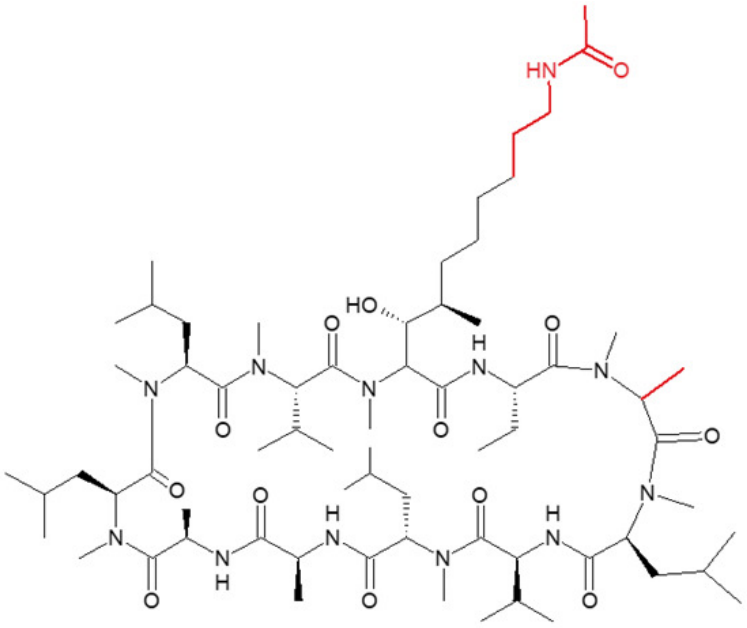
[0005] In one example, the present disclosure provides a self-microemulsifying drug delivery system (SMEDDS) comprising a derivative or an analog, of cyclosporine A, such as CRV431:

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising:

(a) CRV431 at a concentration of from 10 mg/mL to 90 mg/mL:



(CRV431);

(b) Vitamin E;

(c) glyceryl monolinoleate;

(d) propylene glycol;

(e) diethylene glycol monoethyl ether;

(f) ethanol; and

(g) polyoxyl castor oil, wherein Vitamin E, glyceryl monolinoleate, propylene glycol, diethylene glycol monoethyl ether, ethanol, and polyoxyl castor oil are at a weight ratio, respectively, of 1/1.5/2.5/5/2.4/5.

2. The pharmaceutical composition of claim 1 for use as a medicament.

3. Use of a pharmaceutical composition of claim 1 in the manufacture of a medicament.

4. The pharmaceutical composition of claim 1 for use in the treatment or prevention of a disease in a subject, wherein the disease is liver disease.

5. Use of a pharmaceutical composition of claim 1 in the manufacture of a medicament for the treatment or prevention of a disease in a subject, wherein the disease is liver disease.

6. The pharmaceutical composition for use of claim 4 or the use of claim 5, wherein the

disease is a severe liver disease.

7. The pharmaceutical composition for use of claim 4 or the use of claim 5, wherein the disease is hepatitis B (HBV).
8. The pharmaceutical composition for use of claim 4 or the use of claim 5, wherein the disease is liver fibrosis.
9. The pharmaceutical composition for use of claim 4 or the use of claim 5, wherein the disease is hepatocellular carcinoma.
10. The pharmaceutical composition for use or the use of any one of claims 4-9, wherein an area under curve (AUC) of a plot of a concentration of CRV431 in a blood of the subject over time is from 5000 ng.hr/ml to 150000 ng.hr/ml.
11. The pharmaceutical composition for use or the use of any one of claims 4-10, wherein a maximum concentration (C_{max}) of CRV431 in a blood of the subject is from 1500 ng/ml to 2500 ng/ml.
12. The pharmaceutical composition for use or the use of any one of claims 4-11, wherein a time (T_{max}) to reach a maximum concentration of CRV431 in a blood of the subject is from 0.5 hour to 8 hours.
13. The pharmaceutical composition for use or the use of any one of claims 4-12, wherein an elimination half-life ($T_{1/2}$) of CRV431 in a blood of the subject is from 10 hours to 200 hours.
14. The pharmaceutical composition for use or the use of any one of claims 4-13, wherein a concentration of CRV431 in a liver of the subject relative to a concentration of CRV431 in a blood of the subject is from 1 to 20.
15. The pharmaceutical composition for use or the use of any one of claims 4-14, wherein a therapeutically effective amount of the pharmaceutical composition is from 0.5 mg/kg to 5 mg/kg.
16. The pharmaceutical composition for use or the use of any one of claims 4-15, thereby a symptom of the disease in the subject is alleviated and/or a severity of the disease in the subject decreases.
17. The pharmaceutical composition for use or the use of any one of claims 4-16, thereby a function of a liver of the subject is improved.
18. The pharmaceutical composition for use or the use of any one of claims 4-17, thereby a

load of a virus causing the disease decreases.

19. The pharmaceutical composition for use or the use of any of the preceding claims, wherein the pharmaceutical composition is stable at room temperature.

20. The pharmaceutical composition for use or the use of any of the preceding claims, wherein the pharmaceutical composition is stable for from at least 25 days to at least 200 days.

21. The pharmaceutical composition for use or the use of any of the preceding claims, wherein the diameter of particles formed by the pharmaceutical composition dispersed in an aqueous solution is from 15 nm to 40 nm.

22. The pharmaceutical composition for use or the use of any of the preceding claims, wherein the concentration of CRV431 is from 50 mg/mL to 90 mg/mL, optionally wherein the concentration of CRV431 is 70 mg/mL.