such as cyclooxygenase-2 (COX-2), one of the enzymes that converts arachidonic acid to prostaglandin H2 (PGH2). These factors induce inflammation in various tissues. In addition, depending upon the cellular context and the NF-κB nuclear factors released, NF-κB can cause the expression of anti-inflammatory genes. Though these pathways are essential to organism survival and adaptation, chronic activation of the NF-κB system results in uncontrolled inflammatory pathology. Such is the case in dystrophin-deficient muscle, where chronic activation of NF-κB occurs in the muscle of dystrophic mice and DMD patients.

[0005] In DMD patients, the activation of NF-κB typically is observed in muscle tissue prior to the onset of other clinical manifestations. In addition, the immune cells and degenerating muscle fibers of DMD patients show elevated levels of activated NF-κB. Evidence also suggests that mechanical stress activates NF-κB in muscle and drives NF-κB mediated inflammation. More rapid deterioration of muscle is observed in muscles with increased mechanical stress and inflammation, for example, quadriceps and hamstrings.

[0006] Edasalonexent is an orally bioavailable NF-κB inhibitor that comprises a polyunsaturated fatty acid (PUFA) and salicylic acid, which individually inhibit the activation of NF-κB, conjugated together by a linker that is only susceptible to hydrolysis by intracellular fatty acid hydrolase. These compounds have been shown to inhibit NF-κB activation *in vitro*, and that long-term treatment improves the phenotype of both the *mdx* mouse and golden retriever muscular dystrophy (GRMD) dog models of DMD (Hammers *et al*. (2016) JCI INSIGHT 1(21):e90341).

[0007] Despite advances to date, there remains a need for improved methods for treating muscular dystrophy, such as DMD, in patients, including methods for treating DMD with NF-kB inhibitors.

SUMMARY

[0007a] In one aspect, the present disclosure refers to a use of a compound having the structure of Formula I,



(Formula I),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating muscular dystrophy in a subject in need thereof, wherein the medicament is to be administered to the subject in a dosing regimen effective to achieve a threshold plasma concentration of the compound in the subject of at least about 20 ng/ml for least 12 hours in a 24 hour period.

[0007b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising 50-70% by weight of a compound having the structure of Formula I,



(Formula I),

or a pharmaceutically acceptable salt thereof, and optionally one, two, three, or four of: a solvent or diluent; a surfactant; a co-solvent; and an anti-oxidant.

[0008] The present disclosure provides methods and compositions for treating a muscular dystrophy, *e.g.*, Duchenne muscular dystrophy (DMD). The present disclosure is based, in part, upon the discovery that when treating DMD in a subject with a fatty acid acetylated salicylate, *e.g.*, edasalonexent, efficacy is driven by the amount of time that the fatty acid acetylated salicylate is at or above a threshold plasma concentration in the subject, rather than the maximum concentration of the fatty acid acetylated salicylate in the plasma or total exposure to the fatty acid acetylated salicylate.

[0009] Accordingly, in one example, the present disclosure provides a method of treating muscular dystrophy, *e.g.*, Duchenne muscular dystrophy (DMD), in a subject in need thereof. The method comprises administering to the subject a dosing regimen of a compound having the structure of Formula I,



(Formula I),

or a pharmaceutically acceptable salt thereof, effective to achieve a threshold plasma concentration of the compound in the subject of at least about 20 ng/ml for least 12 hours in a 24 hour period. In certain examples, the threshold plasma concentration is from about 20 ng/ml to about 200 ng/ml. In certain examples, the compound is at or above the threshold concentration for at least about 13 hours, about 14 hours, about 15 hours, about 16 hours, about 17 hours, about 18 hours, about 19 hours, about 20 hours, about 21 hours, about 22 hours, about 23 hours, or about 24 hours in a 24 hour period.

[0010] In certain examples, the dosing regimen comprises one, two or three doses of the compound per day. In certain examples, each dose comprises from about 25 mg/kg to about 100 mg/kg of the compound. In certain examples, each dose comprises from about 25 mg/kg to about 50 mg/kg of the compound. In certain examples, each dose comprises from about 20 mg/kg to about 40 mg/kg of the compound. In certain examples, the total daily dosage comprises from about 100 mg/kg to about 200 mg/kg, or from about 100 mg/kg to about 150 mg/kg, *e.g.*, 100 mg/kg or 133 mg/kg. In certain examples, the total daily dosage comprises about 100 mg/kg. In certain examples, the total daily dosage comprises from about 90 mg/kg to about 110 mg/kg. In certain examples, the total daily dosage comprises 100 mg/kg ± 5%, 100 mg/kg ± 10%, 100 mg/kg ± 15%, or 100 mg/kg ± 20% of the compound.

[0011] In certain examples, the dosing regimen comprises three doses per day. In certain examples, the three doses comprise equal amounts of the compound, *e.g.*, each dose comprises from about 25 mg/kg to about 50 mg/kg of the compound, or *e.g.*, each dose comprises about 33 mg/kg of the compound.

[0012] In certain examples, the first dose and the second dose comprise a smaller amount of the compound than the third dose, *e.g.*, the first dose and the second dose comprise about half the amount of the compound as the third dose. For example, in certain examples,

the first dose and the second dose comprise from about 25 mg/kg to about 50 mg/kg of the compound, and the third dose comprises from about 50 mg/kg to about 100 mg/kg of the compound, *e.g.*, the first dose and the second dose comprise about 33 mg/kg of the compound and the third dose comprises about 67 mg/kg of the compound.

[0013] In certain examples, at least one of the three doses is a different amount from the other two doses, *e.g.*, each dose comprises from about 25 mg/kg to about 50 mg/kg of the compound, or *e.g.*, each dose comprises from about 20 mg/kg to about 40 mg/kg of the compound. In one example, two doses are the same and one is different. In one example, all three doses are different.

[0014] In certain examples, the three doses are equal and are administered in dosage forms that contain 250 mg or 100 mg of the compound of Formula I. In certain other examples, the three dosages are not equal and are administered in dosage forms that contain 250 mg or 100 mg of the compound of Formula I, *e.g.*, two are equal and one is different or *e.g.*, each dose is different. In certain examples, the three doses equal a total daily dose of 100 mg/kg ± 5%, 100 mg/kg ± 10%, 100 mg/kg ± 15%, or 100 mg/kg ± 20% of the compound. In certain examples, two doses are 750 mg and one dose is 500 mg. In certain examples, the total daily dose does not exceed 6,000 mg.

[0015] In certain examples, the first dose is administered in the morning, the second dose is administered at mid-day, and the third dose is administered in the evening. In certain examples, each dose is administered with food, *e.g.*, at the time of a meal. For example, in certain examples, the first dose is administered at the time of breakfast, the second dose is administered at the time of lunch, and the third dose is administered at the time of dinner. In certain examples, two doses are administered with breakfast and dinner that are larger than the dose administered with lunch. In certain examples, the dose is administered with food or a meal containing at least 8 g of fat.

[0016] In certain examples, the compound is administered in a pharmaceutical composition, *e.g.*, a composition comprising 50-70% by weight of the compound. The composition may, *e.g.*, further comprise one or more of glyceryl monooleate (type 40), polysorbate 80, polyethylene glycol 400, or DL-α-tocopherol. In certain examples, the composition is formulated as a capsule. In certain examples, the compound is administered orally.

[0017] In certain examples, the method reduces inflammation in quadriceps muscle by at least 20%, and/or reduces fibrosis in quadriceps muscle by at least 20%.

[0018] In another example, the present disclosure provides a pharmaceutical composition comprising 50-70% by weight of a compound having the structure of Formula I,



(Formula I);

or a pharmaceutically acceptable salt thereof, and optionally one, two, three, or four of: a solvent or diluent (*e.g.*, glyceryl monooleate (type 40)); a surfactant (*e.g.*, a nonionic surfactant, *e.g.*, polysorbate 80); a co-solvent (*e.g.*, polyethylene glycol 400); and an anti-oxidant (*e.g.*, DL-α-tocopherol). In certain examples, the solvent or diluent is glyceryl monooleate (type 40). In certain examples, the surfactant is a non-ionic surfactant, *e.g.*, polysorbate 80. In certain examples, the so-solvent is polyethylene glycol. In certain examples, the anti-oxidant is DL-α-tocopherol.

[0019] Various examples of the present disclosure are described in more detail below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, illustrative methods and materials are now described. Other features, objects, and advantages of the present disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise.

BRIEF DESCRIPTION OF THE FIGURES

[0020] **FIGURE 1** shows line graphs of the concentration level of edasalonexent in the plasma and skeletal muscle of C57BL/6 mice that received a dose of 1.5% edasalonexent in their diet.

[0021] **FIGURE 2** is a line graph showing the plasma concentration level of edasalonexent in C57BL/6 mice that received a single oral daily dose of 450 mg/kg edasalonexent, three oral daily doses of 150 mg/kg edasalonexent (for a total daily dose of 450 mg/kg), or two oral daily doses of 150 mg/kg edasalonexent and one oral daily dose of 300 mg/kg edasalonexent (for a total daily dose of 600 mg/kg).

[0022] **FIGURE 3** shows bar graphs depicting quadriceps muscle inflammation (left) and fibrosis (right) in *mdx* mice that received a dose of 1% edasalonexent in their diet.

What is claimed is:

1. Use of a compound having the structure of Formula I,



(Formula I),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating muscular dystrophy in a subject in need thereof, wherein the medicament is to be administered to the subject in a dosing regimen effective to achieve a threshold plasma concentration of the compound in the subject of at least about 20 ng/ml for least 12 hours in a 24 hour period.

2. The use of claim 1, wherein the threshold plasma concentration is from about 20 ng/ml to about 200 ng/ml.

3. The use of claim 1 or 2, wherein the compound is at or above the threshold concentration for at least about 13 hours, about 14 hours, about 15 hours, about 16 hours, about 17 hours, about 18 hours, about 19 hours, about 20 hours, about 21 hours, about 22 hours, about 23 hours, or about 24 hours in a 24 hour period.

4. The use of any one of claims 1-3, wherein the dosing regimen comprises one, two or three doses of the compound per day.

5. The use of claim 4, wherein each dose comprises from about 25 mg/kg to about 100 mg/kg of the compound.

6. The use of any one of claims 1-5, wherein the total daily dosage comprises from about 100 mg/kg to about 200 mg/kg, or from about 100 mg/kg to about 150 mg/kg.

7. The use of claim 6, wherein the total daily dosage comprises about 133 mg/kg.

8. The use of claim 6, wherein the total daily dosage comprises about 100 mg/kg.

9. The use of claim 6, wherein the total daily dosage comprises from about 90 mg/kg to about 110 mg/kg.

10. The use of claim 6, wherein the total daily dosage comprises 100 mg/kg ± 5%, 100 mg/kg ± 10%, 100 mg/kg ± 15%, or 100 mg/kg ± 20%.

11. The use of any one of claims 1-10, wherein the dosing regimen comprises three doses per day.

12. The use of claim 11, wherein the three doses comprise equal amounts of the compound.

13. The use of claim 11 or 12, wherein each dose comprises from about 25 mg/kg to about 50 mg/kg of the compound.

14. The use of claim 11 or 12, wherein each doses comprises from about 20 mg/kg to about 40 mg/kg.

15. The use of any one of claims 12-14, wherein each dose comprises about 33 mg/kg of the compound.

16. The use of claim 11, 13 or 14, wherein the first dose and the second dose comprises a smaller amount of the compound than the third dose.

17. The use of any one of claims 11-15, wherein the three doses are equal and are to be administered in dosage forms that contain 250 mg or 100 mg of the compound of Formula I.

18. The use of claim 17, wherein the three doses equal a total daily dose of 100 mg/kg ± 5%, 100 mg/kg ± 10%, 100 mg/kg ± 15%, or 100 mg/kg ± 20%.

19. The use of claims 17 or 18, wherein the total daily dose does not exceed 6,000 mg.

20. The use of any one of claims 11-19, wherein the first dose is to be administered in the morning, the second dose is to be administered at mid-day, and the third dose is to be administered in the evening.

21. The use of any one of claims 4-20, wherein each dose is to be administered with food.

22. The use of claim 20, wherein each dose is to be administered at the time of a meal.

23. The use of claim 20, wherein the first dose is to be administered at the time of breakfast, the second dose is to be administered at the time of lunch, and the third dose is to be administered at the time of dinner.

24. The use of claim 23, wherein two doses are to be administered with breakfast and dinner that are larger than the dose to be administered with lunch.

25. The use of any one of claims 4-24, wherein the dose is taken with food containing at least 8 g of fat.

26. The use of any one of claims 1-25, wherein the compound is to be administered in a pharmaceutical composition.

27. The use of claim 26, wherein the composition further comprises one or more of glyceryl monooleate (type 40), polysorbate 80, polyethylene glycol 400, or DL-α-tocopherol.

28. The use of claim 26, wherein the composition comprises 50-70% by weight of the compound.

29. The use of any one of claims 26-28, wherein the composition is formulated as a capsule.

30. The use of any one of claims 1-29, wherein the compound is to be administered orally.

31. The use of any one of claims 1-30, wherein the use reduces inflammation in quadriceps muscle by at least 20%.

32. The use of any one of claims 1-31, wherein the use reduces fibrosis in quadriceps muscle by at least 20%.

33. The use of any one of claims 1-32, wherein the muscular dystrophy is Duchenne muscular dystrophy (DMD).

34. The use of any one of claims 1-33, wherein the subject is human.

35. A pharmaceutical composition comprising 50-70% by weight of a compound having the structure of Formula I,



(Formula I),

or a pharmaceutically acceptable salt thereof, and optionally one, two, three, or four of: a solvent or diluent; a surfactant; a co-solvent; and an anti-oxidant.

36. The pharmaceutical composition of claim 35, wherein the solvent or diluent is glyceryl monooleate (type 40).

37. The pharmaceutical composition of claim 35 or 36, wherein the surfactant is a non-ionic surfactant.

38. The pharmaceutical composition of claim 37, wherein the non-ionic surfactant is polysorbate 80.

39. The pharmaceutical composition of any one of claims 35-38, wherein the co-solvent is polyethylene glycol 400.

40. The pharmaceutical composition of any one of claims 35-39, wherein the anti-oxidant is DL-α-tocopherol.