SUMMARY

[0007] The present disclosure is based, in part, on the development of solid oral dosage forms of decitabine and cedazuridine, wherein the solid oral dosage form upon daily administration to a subject provides plasma levels of decitabine with a 5-day area under the curve (AUC) for decitabine that is equivalent to the 5-day AUC for a daily intravenous (IV) dose of decitabine of 20 mg/m^2 administered as a one hour infusion. In some examples, upon daily administration of such solid oral dosage form to a subject, the ratio of AUC for decitabine on day 2 versus day 1 is about 1.5:1 to about 2:1.

[0008] Another aspect of the disclosure refers to solid oral dosage forms comprising decitabine and cedazuridine wherein the solid oral dosage forms upon daily administration to a subject provide a pharmacodynamic effect that is equivalent to the pharmacodynamic effect for a daily intravenous dose of decitabine of 20 mg/m^2 administered as a one hour infusion. In particular examples, the pharmacodynamic effect is DNA demethylation.

[0009] An additional aspect of the disclosure refers to use of the solid oral dosage form disclosed herein in the manufacture of a medicament for treating a disorder that is treatable with decitabine in a subject in need thereof. In another example, there are described methods for treating a disorder in a subject in need thereof, comprising administering to the subject a solid oral dosage form disclosed herein, thereby treating cancer in the subject. In some examples, the disorder is cancer.

[0010] A further aspect of the disclosure refers to use of the solid oral dosage form disclosed herein in the manufacture of a medicament for inhibiting degradation of decitabine in a subject in need thereof. In another example, there are described methods for inhibiting degradation of decitabine in a subject in need thereof, comprising administering to the subject a solid oral dosage form disclosed herein, thereby inhibiting degradation of the decitabine in the subject.

[0011] Another aspect of the disclosure refers to use of the solid oral dosage form disclosed herein in the manufacture of a medicament for reducing DNA methylation in a subject in need thereof. In another example, there are described methods of reducing DNA methylation (*e.g.*, LINE-1 methylation) in a subject in need thereof, comprising administering to the subject a solid oral dosage form according to an embodiment of the invention, thereby reducing DNA methylation in the subject.

[0012] In another example, there is disclosed the use of a solid oral dosage form according to an embodiment of the invention in methods for treating a disorder, methods for inhibiting degradation of decitabine, and methods of reducing DNA methylation (*e.g.*, LINE-1 methylation).

[0013] These and other aspects of the invention are set forth in more detail in the description of the invention below.

What is claimed is:

1. A solid oral dosage form comprising cedazuridine and decitabine, wherein the solid oral dosage form upon daily administration to a human provides plasma levels of decitabine with a 5-day AUC for decitabine that is equivalent to the 5-day AUC for a daily intravenous dose of decitabine of 20 mg/m^2 administered as a 1 h infusion.

2. The solid oral dosage form of claim 1, wherein upon daily administration to a human the ratio of AUC for decitabine on day 2 versus day 1 is about 1.5:1 to about 2:1.

3. The solid oral dosage form of claim 1 or 2, wherein the solid oral dosage form upon daily administration to a human provides a pharmacodynamic effect that is equivalent to the pharmacodynamic effect for a daily intravenous dose of decitabine of 20 mg/m^2 administered as a 1 h infusion.

4. The solid oral dosage form of claim 3, wherein the pharmacodynamic effect is DNA demethylation.

5. The solid oral dosage form of any one of claims 1-4, which is a tablet.

6. The solid oral dosage form of any one of claims 1-4, which is a capsule.

7. The solid oral dosage form of any one of claims 1-6, comprising decitabine and cedazuridine in a weight ratio of about 30:100 to about 40:100.

8. The solid oral dosage form of claim 7, comprising decitabine and cedazuridine in a weight ratio of about 35:100.

9. The solid oral dosage form of any one of claims 1-8, comprising about 100 mg cedazuridine.

10. The solid oral dosage form of any one of claims 1-9, comprising about 35 mg decitabine.

11. The solid oral dosage form of any one of claims 1-10, further comprising one or more of a diluent, binder, disintegrant, glidant, or lubricant.

12. The solid oral dosage form of any one of claims 1-11, further comprising a diluent, binder, disintegrant, glidant, and lubricant.

13. The solid oral dosage form of claim 11 or 12, wherein the diluent comprises at least one of lactose, lactose monohydrate, cellulose, sorbitol, dibasic calcium phosphate dehydrate, and calcium sulfate dehydrate.

14. The solid oral dosage form of any one of claims 11-13, wherein the binder comprises at least one of gelatin, glucose, lactose, cellulose, methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, starch, poly vinyl pyrrolidone, sodium alginate, carboxymethylcellulose, and acacia.

15. The solid oral dosage form of any one of claims 11-14, wherein the disintegrant comprises at least one of croscarmellose sodium, crospovidone, sodium starch glycollate, and starch.

16. The solid oral dosage form of any one of claims 11-15, wherein the glidant comprises at least one of colloidal silicon dioxide, cornstarch, and talc.

17. The solid oral dosage form of any one of claims 11-16, wherein the lubricant comprises at least one of stearic acid, magnesium stearate, calcium stearate, talc, paraffin, sodium lauryl sulphate, sodium benzoate, and polyethylene glycol.

18. The solid oral dosage form of any one of claims 1-17, further comprising lactose monohydrate, hydroxypropyl methylcellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

19. The solid oral dosage form of any one of claims 1-18, further comprising a coating.

20. The solid oral dosage form of claim 19, wherein the coating is a color coating.

21. Use of the solid oral dosage form of any one of claims 1-20 in the manufacture of a medicament for treating a disorder that is treatable with decitabine in a subject in need thereof.

22. The use of claim 21, wherein the disorder that is treatable with decitabine is a hyperproliferative disorder.

23. The use of claim 21, wherein the disorder that is treatable with decitabine is a cancer.

24. The use of claim 23, wherein the cancer is selected from hematological cancers and solid cancers.

25. The use of claim 24, wherein the hematological cancer is selected from myelodysplastic syndromes (MDS), leukemia, and lymphoma.

26. The use of claim 25, wherein the leukemia is acute lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, myeloproliferative neoplasms, or chronic myelomonocytic leukemia.

27. The use of claim 25, wherein the lymphoma is Hodgkin's Lymphoma, Non-Hodgkin lymphoma, or T-cell lymphoma.

28. The use of claim 25, wherein the myelodysplastic syndromes (MDS) is lower risk MDS (*e.g.*, IPSS low and/or IPSS intermediate 1).

29. The use of claim 24, wherein the solid cancer is selected from pancreatic cancer, ovarian cancer, peritoneal cancer, non-small cell lung cancer, breast cancer, neuroectodermal tumors, and sarcomas.

30. The use of any one of claims 21-29, wherein the solid oral dosage form is to be administered about 1 day to about 28 days per 28-day cycle (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 days per 28-day cycle).

31. The use of any one of claims 21-30, wherein the solid oral dosage form is to be administered on consecutive days per 28-day cycle (*e.g.*, 3 days MTW, TWTh, WThF, *etc.*; 5 days MTWThF, *etc.*; 7 days, MTWThFSS); 14 days (*e.g.*, two consecutive weeks); 21 days (*e.g.*, three consecutive weeks).

32. The use of any one of claims 21-30, wherein the solid oral dosage form is to be administered on non-consecutive days per 28-day cycle (*e.g.*, 3 days MWF; 10 days (5d on, 2d off, 5d on); 14 days (7d on, 7d off, 7d on).

33. The use of any one of claims 21-30, wherein the solid oral dosage form is to be administered for one week per 28-day cycle.

34. The use of any one of claims 21-30, wherein the solid oral dosage form is to be administered for two weeks (*e.g.*, consecutive, *e.g.*, non-consecutive) per 28-day cycle.

35. The use of any one of claims 21-30, wherein a solid oral dosage form is to be administered for three weeks (*e.g.*, consecutive, *e.g.*, non-consecutive) per 28-day cycle.

36. The use of any one of claims 21-30, wherein the solid oral dosage form is to be administered for four weeks per 28-day cycle.

37. Use of the solid oral dosage form of any one of claims 1-20 in the manufacture of a medicament for reducing DNA methylation in a subject in need thereof.

38. Use of the solid oral dosage form of any one of claims 1-20 in the manufacture of a medicament for inhibiting degradation of decitabine in a subject in need thereof.