[0004] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

BRIEF SUMMARY

[0004a] In an aspect of the present disclosure, there is provided a delayed sustained-release oral drug dosage form of a Janus kinase (JAK) inhibitor, the delayed sustained-release oral drug dosage form comprising:

a sustained-release drug component comprising a first erodible material admixed with the JAK inhibitor; and

a delay component,

wherein the delay component prevents the release of the JAK inhibitor from the delayed sustained-release oral drug dosage form for about 2 hours to about 6 hours after the delayed sustained-release oral drug dosage form is to be administered to a human individual.

[0004b] In another aspect of the present disclosure, there is provided a method for preparing a delayed sustained-release tofacitinib oral drug dosage form by three-dimensional (3D) printing,

wherein the delayed sustained-release tofacitinib oral drug dosage form comprises a shell containing an insoluble material, a pharmaceutical core containing tofacitinib, and a delay member without tofacitinib,

the method comprising dispensing materials according to a layer-by-layer model of the delayed sustained-release oral drug dosage form to print the delayed sustained-release oral drug dosage form, wherein each layer of the layer-by-layer model is printed by dispensing, as necessary, for a layer:

(a) a pharmaceutical core containing tofacitinib;

(b) the delay member without tofacitinib; and

(c) the shell comprising an insoluble material.

[0004c] In a further aspect of the present disclosure, there is provided a method of injection molding an oral drug dosage form disclosed herein, the method comprising:

(a) injecting a hot melt of the shell material into a mold cavity to form the shell;

(b) injecting a hot melt of the first erodible material admixed with a JAK inhibitor into the shell to form the sustained-release drug component; and

(c) injecting a hot melt of the second erodible material not admixed with the JAK inhibitor into the shell to form the delay member.

[0004d] In another aspect of the present disclosure, there is provided a use of a delayed sustained-release oral drug dosage form disclosed herein, in the manufacture of a medicament for preventing morning stiffness caused by rheumatoid arthritis, or psoriatic arthritis, wherein the delayed sustained-release oral drug dosage form is to be administered within about 1 hour of going to bed.

[0004e] In a further aspect of the present disclosure, there is provided a delayed sustained-release oral drug dosage form disclosed herein, for use in therapy.

[0005] In some examples, provided herein is a delayed sustained-release oral drug dosage form of a Janus kinase (JAK) inhibitor, the delayed sustained-release oral drug dosage form comprising: a sustained-release drug component comprising a first erodible material admixed with the JAK inhibitor; and a delay component, wherein the delay component prevents the release of the JAK inhibitor from the delayed sustained-release oral drug dosage form for about 2 hours to about 6 hours after administration of the delayed sustained-release oral drug dosage form to a human individual.

[0006] In some examples, the delay component comprises: a delay member comprising a second erodible material not admixed with the JAK inhibitor; and a shell, wherein the delay component completely surrounds the sustained-release drug component. In some examples, the sustained-release drug component is a layer having a top surface and a bottom surface. In some examples, the top surface of the sustained-release drug component is not flat. In some examples, the thickness as measured between the top surface and the bottom surface is substantially consistent.

[0007] In some examples, the sustained-release drug component is embedded in the shell such that the bottom surface and a side surface of the sustained-release drug component are in direct contact with the shell.

[0008] In some examples, the top surface of the sustained-release drug component is not in direct contact with the shell.

[0009] In some examples, the delay member is a layer having a top surface and a bottom surface. In some examples, the top surface of the delay member is not flat. In some examples, the thickness as measured between the top surface and the bottom surface is substantially consistent.

[0010] In some examples, the bottom surface of the delay member, or a portion thereof, is in direct contact with the top layer of the sustained-release drug component.

[0011] In some examples, a side of the delay member is in direct contact with the shell.

[0012] In some examples, a portion of the bottom surface of the delay member is in direct contact with the shell. In some examples, the portion of the bottom surface of the delay member that is in direct contact with the shell forms a perimeter extending beyond the top surface of the sustained-release drug component.

[0013] In some examples, the delay member and the shell are configured such that the JAK inhibitor is prevented from being released from the delayed sustained-release oral drug dosage form until after the delay member is eroded.

[0014] In some examples, the shell comprises an insulating material that is impermeable to bodily fluids. In some examples, the insulating material is a non-erodible material. In some examples, the insulating material is an erodible material having a pH-sensitive erosion and/or an erosion rate that allows for the complete release of the JAK inhibitor from the delayed sustained-release oral drug dosage form prior to exposure of the sustained-release drug component to bodily fluids due to erosion of the shell.

[0015] In some examples, the delayed sustained-release oral drug dosage form has a substantially planar top surface. In some examples, the top surface is formed by the delay member and the shell. In some examples, the shell comprises an inset having a depth, wherein the delay member is configured to fit in the inset of the shell. In some examples, the thickness of the delay member is the same as the depth of the inset of the shell. In some examples, the top surface is a capsule shape.

[0016] In some examples, the top surface of the sustained-release drug component is a capsule shape.

[0017] In some examples, the top surface of the delay member is a capsule shape.

[0018] In some examples, the delay component prevents the release of the JAK inhibitor from the delayed sustained-release oral drug dosage form for about 2 hours to about 4 hours after administration of the delayed sustained-release oral drug dosage form to a human individual.

[0019] In some examples, the delay component prevents the release of the JAK inhibitor from the delayed sustained-release oral drug dosage form for about 2 hours to about 3 hours after administration of the delayed sustained-release oral drug dosage form to a human individual.

[0020] In some examples, the sustained-release drug component is configured to release the JAK inhibitor from the delayed sustained-release oral drug dosage form according to the following: (i) not more than 30% of the total JAK inhibitor is released at 1 hour after complete erosion of the delay component or a portion thereof; (ii) not less than 35% and not more than 75% of the total JAK inhibitor is released at 2.5 hours after complete erosion of the delay component or a portion thereof; and (iii) not less than 75% of the total JAK inhibitor is released at 5 hours after complete erosion of the delay component or a portion thereof.

[0021] In some examples, the release of the JAK inhibitor is based on an *in vitro* release rate.

[0022] In some examples, when administered to the human individual, the mean area under the plasma concentration versus time curve after complete erosion of the delay component or a portion thereof is about 17 ng-hr/mL per mg JAK inhibitor dosed to about 42 ng-hr/mL per mg of JAK inhibitor dosed.

[0023] In some examples, the T_{max} occurs within about 6 hours after complete erosion of the delay component or a portion thereof.

[0024] In some examples, when administered to the human individual, the ratio of geometric mean plasma C_{max} to C_{min} is about 10 to about 100.

[0025] In some examples, the release of the JAK inhibitor is based on an *in vitro* dissolution technique comprising use of a USP rotating paddle apparatus rotated at about 50 RPM and a test medium comprising 900 mL of 0.05 M potassium phosphate buffer at pH 6.8 and 37 °C.

[0026] In some examples, the top surface of the sustained-release drug component has a surface area of about 20 mm^2 to about 400 mm^2.

[0027] In some examples, the top surface of the sustained-release drug component has a largest crossing dimension of about 5 mm to about 20 mm.

[0028] In some examples, the top surface of the sustained-release drug component has a crossing dimension perpendicular to a largest crossing dimension of about 2 mm to about 20 mm.

[0029] In some examples, the sustained-release drug component has a thickness of about 0.2 mm to about 5 mm.

[0030] In some examples, the sustained-release drug component has a drug mass fraction (m_F) of the JAK inhibitor of about 0.2 to about 0.6.

[0031] In some examples, the sustained-release drug layer has an *in vitro* dissolution rate of about 2% per hour to about 40% per hour based on an *in vitro* dissolution technique comprising use of a USP rotating paddle apparatus rotated at about 50 RPM and a test medium comprising 900 mL of 0.05 M potassium phosphate buffer at pH 6.8 and 37 °C.

[0032] In some examples, the first erodible material of the sustained-release drug component comprises one or more of hydroxypropyl cellulose (HPC EF), vinylpyrrolidone-vinyl acetate copolymer (VA64), triethyl citrate (TEC), and glycerin.

[0033] In some examples, the first erodible material of the sustained-release drug component comprises HPC EF at about 35 w/w% to about 45 w/w%, VA64 at about 5 w/w% to about 15 w/w%, and glycerin at about 10 w/w% to about 20 w/w%.

[0034] In some examples, the top surface of the delay member has a surface area of about 20 mm^2 to about 400 mm^2.

[0035] In some examples, the top surface of the delay member has a largest crossing dimension of about 5 mm to about 20 mm.

[0036] In some examples, the top surface of the delay member has a crossing dimension perpendicular to a largest crossing dimension of about 2 mm to about 20 mm.

[0037] In some examples, the delay member has a thickness of about 0.2 mm to about 5 mm.

[0038] In some examples, the delay completely dissolves with in about 6 hours after administration of the delayed sustained-release oral drug dosage form to the human individual.

[0039] In some examples, the second erodible material of the delay layer comprises one or more of hydroxypropyl cellulose (HPC EF), triethyl citrate (TEC), and titanium dioxide.

[0040] In some examples, the delay layer comprises HPC EF at about 80 w/w% to about 90 w/w%, TEC at about 10 w/w% to about 20 w/w%, and titanium dioxide at about 0.1 w/w% to about 0.3 w/w%.

[0041] In some examples, the shell has a largest crossing dimension of about 5 mm to about 20 mm.

[0042] In some examples, the shell has a crossing dimension perpendicular to a largest crossing dimension of about 5 mm to about 20 mm.

[0043] In some examples, the delayed sustained-release oral drug dosage form has a thickness of about 0.2 mm to about 15 mm.

[0044] In some examples, the shell has a minimum thickness of at least about 0.4 mm.

[0045] In some examples, the shell comprises one or more of ammonio methacrylate copolymer type B, ethylcellulose, stearic acid, and titanium dioxide.

[0046] In some examples, the shell comprises ammonio methacrylate copolymer type B at about 60 w/w% to about 70 w/w%, ethylcellulose at about 10 w/w% to about 20 w/w%, stearic acid at about 15 w/w% to about 25 w/w%, and titanium dioxide at about 0.1 w/w/% to about 0.3 w/w%.

[0047] In some examples, the JAK inhibitor interferes with the JAK-STAT signaling pathway. In some examples, wherein the JAK inhibitor is an inhibitor of any one or more of JAK1, JAK2, JAK3, or TYK2.

[0048] In some examples, the JAK inhibitor is tofacitinib or a pharmaceutically acceptable salt thereof. In some examples, the JAK inhibitor is tofacitinib citrate.

[0049] In some examples, the amount of the JAK inhibitor in the delayed sustained-release oral drug dosage form is about 11 mg.

[0050] In some examples, the amount of the JAK inhibitor in the delayed sustained-release oral drug dosage form is about 22 mg.

[0051] In some examples, the delayed-sustained-release oral drug dosage form is not an osmotic-controlled release oral drug dosage form.

[0052] In other examples, provided herein is a commercial batch of any delayed sustained-release oral drug dosage form described herein, wherein the commercial batch has a standard deviation of about 0.05 or less for each of the following: an amount of a JAK inhibitor in the delayed sustained-release oral drug dosage form; weight of the delayed sustained-release oral drug dosage form; a largest crossing dimension of the delayed sustained-release oral drug dosage form; and a crossing dimension perpendicular to the largest crossing dimension of the delayed sustained-release oral drug dosage form.

[0053] In some examples, the commercial batch comprises at least about 1000 of the delayed sustained-release oral drug dosage forms.

[0054] In other examples, provided herein is a method of three-dimensional (3D) printing of any delayed sustained-release oral drug dosage form described herein, the method comprising: (a) dispensing the delay component or a portion thereof; and (b) dispensing the sustained-release drug component comprising the first erodible material admixed with the JAK inhibitor.

[0055] In some examples, dispensing the delay component comprises: (i) dispensing the shell; and (ii) dispensing the delay member comprising the second erodible material not admixed with the JAK inhibitor.

[0056] In some examples, the dispensing is via melt extrusion deposition (MED).

[0057] In some examples, the dispensing of the delay component, dispensing of the shell, and dispensing of the delay member are performed by a different printing head.

[0058] In other examples, provided herein is a method for preparing a delayed sustained-release tofacitinib oral drug dosage form by three-dimensional (3D) printing, wherein the delayed sustained-release tofacitinib oral drug dosage form comprises a shell containing an insoluble material, a pharmaceutical core containing tofacitinib, and a delay member without tofacitinib, the method comprising: (a) dispensing the insoluble material to form the shell; (b) dispensing the core material containing tofacitinib; and (c) dispensing the delay member without tofacitinib.

[0059] In some examples, the dispensing is via melt extrusion deposition (MED).

[0060] In some examples, the dispensing of each material is performed by a different printing head.

[0061] In other examples, provided herein is a method of injection molding any oral drug dosage form described herein, the method comprising: (a) injecting a hot melt of the shell material into a mold cavity to form the shell; (b) injecting a hot melt of the first erodible material admixed with a JAK inhibitor into the shell to form the sustained-release drug component; and (c) injecting a hot melt of the second erodible material not admixed with the JAK inhibitor into the shell to form the delay member.

[0062] In other examples, provided herein is a method of injection molding any delayed sustained-release oral drug dosage form described herein, the method comprising: (a) hot melting a shell material, a first erodible material admixed with a JAK inhibitor, and a second erodible material not admixed with the JAK inhibitor; (b) delivering each material to the respective injection unit; (c) injecting a hot melt of the shell material into a mold cavity to form the shell; (d) allowing the shell to cool and opening the mold to release the shell; (e) transferring the shell to a male mold to inject the first erodible material admixed with the JAK inhibitor to form the sustained-release drug component; (f) injection a hot melt of the first erodible material admixed with the JAK inhibitor to form the sustained-release drug component; (g) allowing the sustained-released drug component to cool and opening the mold to release the shell and the sustained-release drug component; (h) transferring the shell and the sustained-release drug component to a male mold to inject the second erodible material not admixed with the JAK inhibitor to form the delay member; (i) injection a holt melt of the second erodible material not admixed with the JAK inhibitor; and (j) ejecting the delayed sustained-release oral drug dosage form.

[0063] In some examples, the injection unit is selected from the group consisting of a single screw injection unit, a plunger injection unit, and a gear pump injection unit. In some examples, step (c) to step (j) are performed in series. In some examples, step (c), step (f), and step (i) are performed at the same time. In some examples, step (e), step (h), and step (j) are performed at the same time.

[0064] In other examples, provided herein is a method for preventing morning stiffness caused by rheumatoid arthritis, the method comprising administering to a human individual a delayed sustained-release oral drug dosage form described herein, wherein the delayed sustained-release oral drug dosage form is administered within about 1 hour of going to bed.

[0065] In other examples, provided herein is a method for preventing morning stiffness caused by psoriatic arthritis, the method comprising administering to a human individual a delayed sustained-release oral drug dosage form described herein, wherein the delayed sustained-release oral drug dosage form is administered within about 1 hour of going to bed.

[0066] In other examples, provided herein is a method for treating ulcerative colitis, the method comprising administering to a human individual a delayed sustained-release oral drug dosage form described herein.

[0067] It will also be understood by those skilled in the art that changes in the form and details of the implementations described herein may be made without departing from the scope of this disclosure. In addition, although various advantages, examples, and objects have been described with reference to various implementations, the scope of this disclosure should not be limited by reference to such advantages, examples, and objects.

BRIEF DESCRIPTION OF THE DRAWINGS

[0068] **FIGS. 1A-1H** show cross-sectional diagrams of exemplary delayed sustained-release oral drug dosage forms.

[0069] **FIGS. 2A-2D** show diagrams of exemplary delayed sustained-release oral drug dosage forms.

[0070] **FIG. 3** shows a dissolution plot for a delayed sustained-release oral drug dosage form and a commercially available extended release dosage form.

[0071] **FIG. 4** shows a dissolution plot for a delayed sustained-release oral drug dosage form and a commercially available extended release dosage form.

CLAIMS

What is claimed is:

1. A delayed sustained-release oral drug dosage form of a Janus kinase (JAK) inhibitor, the delayed sustained-release oral drug dosage form comprising:

    a sustained-release drug component comprising a first erodible material admixed with the JAK inhibitor; and

    a delay component,

        wherein the delay component prevents the release of the JAK inhibitor from the delayed sustained-release oral drug dosage form for about 2 hours to about 6 hours after the delayed sustained-release oral drug dosage form is to be administered to a human individual.

2. The delayed sustained-release oral drug dosage form of claim 1, wherein the delay component comprises:

    a delay member comprising a second erodible material not admixed with the JAK inhibitor; and

    a shell,

    wherein the delay component completely surrounds the sustained-release drug component.

3. The delayed sustained-release oral drug dosage form of claim 2, wherein the JAK inhibitor is tofacitinib or a pharmaceutically acceptable salt thereof, wherein the sustained-release drug component is a layer having a top surface and a bottom surface, wherein the thickness as measured between the top surface and the bottom surface is substantially consistent, wherein the sustained-release drug component is embedded in the shell such that the bottom surface and a side surface of the sustained-release drug component are in direct contact with the shell, wherein the top surface of the sustained-release drug component is not in direct contact with the shell.

4. The delayed sustained-release oral drug dosage form of claim 3, wherein the sustained-release drug component has a thickness of about 0.2 mm to about 5 mm.

5. The delayed sustained oral drug dosage form of claim 3, wherein the first erodible material of the sustained-release drug component comprises one or more of hydroxypropyl cellulose (HPC EF), vinylpyrrolidone-vinyl acetate copolymer (VA64), triethyl citrate (TEC), and glycerin.

6. The delayed sustained-release oral drug dosage form of claim 2, wherein the delay member is a layer having a top surface and a bottom surface, wherein the thickness as measured between the top surface and the bottom surface is substantially consistent, wherein the bottom surface of the delay member, or a portion thereof, is in direct contact with the top layer of the sustained-release drug component.
7. The delayed sustained-release oral drug dosage form of claim 6, wherein bottom surface of the delay member is larger than the top surface of the sustained-release drug component.
8. The delayed sustained-release oral drug dosage form of claim 6, wherein the delay member has a thickness of about 0.2 mm to about 5 mm.
9. The delayed sustained-release oral drug dosage form of claim 6, wherein the delay member and the shell are configured such that the JAK inhibitor is prevented from being released from the delayed sustained-release oral drug dosage form until after the delay member is eroded, wherein the delay completely dissolves with in about 6 hours after administration of the delayed sustained-release oral drug dosage form to the human individual.
10. The delayed sustained-release oral drug dosage form of claim 6, wherein the delay component prevents the release of the JAK inhibitor from the delayed sustained-release oral drug dosage form for about 2 hours to about 4 hours after administration of the delayed sustained-release oral drug dosage form to a human individual.
11. The delayed sustained-release oral drug dosage form of claim 6, wherein the second erodible material of the delay layer comprises one or more of hydroxypropyl cellulose (HPC EF), triethyl citrate (TEC), and titanium dioxide.
12. The delayed sustained-release oral drug dosage form of claim 2, wherein the shell comprises an insulating material that is impermeable to bodily fluids.
13. The delayed sustained-release oral drug dosage form of claim 12, wherein the insulating material is a non-erodible material, or wherein the insulating material is an erodible material having a pH-sensitive erosion and/or an erosion rate that allows for the complete release of the JAK inhibitor from the delayed sustained-release oral drug dosage form prior to exposure of the sustained-release drug component to bodily fluids due to erosion of the shell.
14. The delayed sustained-release oral drug dosage form of claim 12, wherein the shell has a minimum thickness of at least about 0.4 mm.

15. The delayed sustained release oral drug dosage form of claim 14, wherein the shell comprises one or more of ammonio methacrylate copolymer type B, ethylcellulose, stearic acid, and titanium dioxide.

16. The delayed sustained-release oral drug dosage form of any one of claims 1-15, wherein the sustained-release drug component is configured to release the JAK inhibitor from the delayed sustained-release oral drug dosage form according to the following:

    (i) not more than 30% of the total JAK inhibitor is released at 1 hour after complete erosion of the delay component or a portion thereof;

    (ii) not less than 35% and not more than 75% of the total JAK inhibitor is released at 2.5 hours after complete erosion of the delay component or a portion thereof; and

    (iii) not less than 75% of the total JAK inhibitor is released at 5 hours after complete erosion of the delay component or a portion thereof.

17. The delayed sustained-release oral drug dosage form of any one of claims 1-15, wherein the T_{max} occurs within about 6 hours after complete erosion of the delay component or a portion thereof.

18. A method for preparing a delayed sustained-release tofacitinib oral drug dosage form by three-dimensional (3D) printing,

    wherein the delayed sustained-release tofacitinib oral drug dosage form comprises a shell containing an insoluble material, a pharmaceutical core containing tofacitinib, and a delay member without tofacitinib,

    the method comprising dispensing materials according to a layer-by-layer model of the delayed sustained-release oral drug dosage form to print the delayed sustained-release oral drug dosage form, wherein each layer of the layer-by-layer model is printed by dispensing, as necessary, for a layer:

    (a) a pharmaceutical core containing tofacitinib;

    (b) the delay member without tofacitinib; and

    (c) the shell comprising an insoluble material.

19. A method of injection molding an oral drug dosage form of any one of claims 1-17, the method comprising:

    (a) injecting a hot melt of the shell material into a mold cavity to form the shell;

    (b) injecting a hot melt of the first erodible material admixed with a JAK inhibitor into the shell to form the sustained-release drug component; and

(c) injecting a hot melt of the second erodible material not admixed with the JAK inhibitor into the shell to form the delay member.

20. Use of a delayed sustained-release oral drug dosage form of any one of claims 1-17, in the manufacture of a medicament for preventing morning stiffness caused by rheumatoid arthritis, or psoriatic arthritis, wherein the delayed sustained-release oral drug dosage form is to be administered within about 1 hour of going to bed.

21. A delayed sustained-release oral drug dosage form of any one of claims 1-17, for use in therapy.