

**ORAL DRUG DOSAGE FORM FOR TARGETED DRUG DELIVERY
BASED ON TRACKING MARKER AND METHODS OF DESIGN AND USE
THEREOF**

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority benefit of International Patent Application No. PCT/CN2023/138397, filed December 13, 2023, the content of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

In some aspects, the present disclosure relates to an oral drug dosage form configured to be used for targeted drug delivery at a desired gastrointestinal location. In other aspects, the present disclosure relates to methods of design and use related to the oral drug dosage form described herein.

BACKGROUND

Oral drug dosage forms provide many benefits to patients, including limiting the number of visits and avoiding more invasive methods of administration, such as injection or rectal administration. Certain drugs benefit from precise drug delivery in the gastrointestinal tract or from maintaining long-term sustained release of the drug in the stomach. For example, delivering to a desired gastrointestinal location or long-term gastric retention can help increase the efficacy by increasing drug concentration at the active site and/or enhancing systemic drug absorption, and can help reduce toxicity, including by avoiding drug exposure to certain gastrointestinal locations and/or limiting systemic drug absorption. The extreme and variable conditions of the gastrointestinal system make precise drug delivery and long-term gastric retention via oral drug dosage forms very challenging. Certain extreme conditions of the gastrointestinal tract include the low pH of the gastric juice and the mechanical stresses associated with swallowing and digesting oral drug dosage forms. In addition, there is a large degree of variability in the movement of substances through the gastrointestinal tract (including in an

individual administered at different times and between different individuals), and important differences between health and disease status are often observed.

In the process of visible oral drug dosage forms, *in vitro* dissolution experiments, animal experiments, and clinical drug trials are the most common methods for verifying the pharmaceutical effects of drugs. None of the three experimental methods above can directly judge the delivery, release location, or release condition of the drug. Therefore, it is important to develop an oral drug dosage form and/or method that can verify whether the drug is precisely located, released at a specific location, or released at a specific time in the gastrointestinal tract.

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

SUMMARY

In some embodiments, the present disclosure provides an oral drug dosage form comprising a drug component, a delay component, and a first tracking marker. The drug component comprises a first erodible material admixed with a drug; the delay component comprises a second erodible material that is not admixed with the drug, and the delay component completely surrounds the drug component; the first tracking marker has at least one face in contact with the delay component and comprises a third erodible material admixed with a first visible material.

In some embodiments, the oral drug dosage form further comprises a second tracking marker, which comprises a fourth erodible material admixed with a second visible material, and the drug component completely surrounds the second tracking marker.

In some embodiments, the drug component further comprises a second tracking marker, and the drug component comprises a first erodible material admixed with a drug and a second visible material.

In some embodiments, the oral drug dosage form further comprises a non-erodible component, which comprises a first non-erodible material that is not admixed with a drug.

In some embodiments, the oral drug dosage form further comprises a third tracking marker, and the non-erodible component completely surrounds the third tracking

marker.

In some embodiments, the first, second, third, and fourth erodible materials may be the same or may be different.

In some embodiments, the first, second, third, and fourth erodible materials may be each simultaneously selected from one or more of the following materials: copovidone, polyvinylpyrrolidone-co-vinyl acetate, polyvinylpyrrolidone-polyvinyl acetate copolymer 60/40, crospovidone, polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose or hypromellose, hydroxypropyl methylcellulose phthalate, methylcellulose, methacrylic acid copolymer, poly(methacrylic acid-co-ethyl acrylate), poly(butyl methacrylate-co-(2-dimethylaminoethyl)methacrylate-co-methyl methacrylate) 1:2:1, poly(dimethylaminoethyl methacrylate-co-methacrylate), poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonium ethyl methacrylate chloride), poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1, poly(methacrylic acid-co-methyl methacrylate) 1:2, poly(methacrylic acid-co-ethyl acrylate) 1:1, poly(methacrylic acid-co-methyl methacrylate) 1:1, polyethylene oxide, polyethylene glycol, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer 57/30/13, polyethylene glycol-polyvinyl alcohol graft copolymer 25/75, Kollicoat IR-polyvinyl alcohol 60/40, polyvinyl alcohol, aminoalkyl methacrylate copolymer E, hydroxypropyl methylcellulose acetate succinate or hypromellose acetate succinate, methacrylate copolymer, ammonio alkyl methacrylate copolymer, ethylcellulose, polyvinyl acetate, polyvinylpyrrolidone 80/20, polyvinylacetal diethylamino lactate, maltitol, lactose monohydrate, xylitol, isomalt, sucrose, glucose, dextran 70, or maltose.

In some embodiments, the first, second, third, and fourth erodible materials may each simultaneously include a plasticizer and/or an additive.

In some embodiments, the plasticizer is any one or more of triethyl citrate, vitamin E polyethylene glycol succinate, acetylated triethyl citrate, tributyl citrate, tributyl *o*-acetyl citrate, polyethylene glycol 15-hydroxystearate, PEG-40 hydrogenated castor oil, polyethylene glycol 35-castor oil, dibutyl sebacate, diethyl phthalate, glycerin, methyl 4-hydroxybenzoate, castor oil, oleic acid, glyceryl triacetate, polyalkylene glycol, stearic acid, palmitic acid, malic acid, polyethylene glycol, lauroyl PEG-32

glyceride, poloxamer 188, poloxamer 407, acetyl tributyl citrate, D-sorbitol, propylene glycol, citric acid, glyceryl behenate, D-mannitol, polysorbate, sorbitan monostearate, sorbitan monooleate, or polyoxyethylene 40 stearate.

In some embodiments, the additive may be a filler, a binder, a lubricant, a glidant, and a disintegrant.

In some embodiments, the delay component comprises: a pH-based enteric member configured to erode at or above a predetermined pH value; and an erodible delay member comprising a second erodible material.

In some embodiments, the first tracking marker has at least one face in contact with the erodible delay member.

In some embodiments, the top surface of the first tracking marker is in contact with the bottom surface of the erodible delay member.

In some embodiments, the non-erodible component comprises a barrier material that is impermeable to bodily fluids.

In some embodiments, the barrier material comprises one or more of ethyl cellulose (EC), dibutyl sebacate (DBS), and titanium dioxide. In some embodiments, the barrier material is a non-erodible material. In some embodiments, the barrier material is an erodible material having pH-based erosion and/or a certain erosion rate that allows complete release of the drug from the oral drug dosage form before the drug component is exposed to bodily fluids due to erosion of the non-erodible component.

In some embodiments, the top or bottom surface of the oral drug dosage form has a shape of a circle, an ellipse, a bullet, an arrow, a triangle, an arc triangle, a square, an arc square, a rectangle, an arc rectangle, a diamond, a pentagon, a hexagon, an octagon, a half-moon, an almond, or a combination thereof.

In some embodiments, the non-erodible component is configured to control the exposure of the drug component and/or the delay component of the oral drug dosage form to bodily fluids.

In some embodiments, the first tracking marker shows a pattern, such as a symmetrical pattern, on at least one projection surface, and/or the second tracking marker shows a pattern, such as a symmetrical pattern, on at least one projection surface.

In some embodiments, the first tracking marker is a loop structure and the second

tracking marker is a strip structure.

In some embodiments, provided is an oral drug dosage form comprising a drug component, a first tracking marker, a second tracking marker, and a cover layer surrounding the drug component, the first tracking marker, and the second tracking marker. The first tracking marker is used for indicating whether the drug component is exposed to bodily fluids, the second tracking marker is used for indicating whether the drug component is completely released, and the cover layer completely or partially consists of an erodible material.

In some embodiments, the first tracking marker and the drug component are exposed to the bodily fluids simultaneously.

In some embodiments, the second tracking marker is covered by the drug component.

In some embodiments, the shape of the surface of the second tracking marker is the same as the shape of the surface of the drug component.

In some embodiments, the second tracking marker is smaller in size than the drug component.

In some embodiments, the cover layer further comprises a non-erodible portion.

In some embodiments, the second tracking marker is covered by the non-erodible portion.

In some embodiments, the first tracking marker is a loop structure.

In some embodiments, provided is an oral drug dosage form comprising a drug component, a drug-free delay component, and a tracking marker. The delay component comprises a pH-based enteric member and/or an erodible delay member and is used for controlling the oral drug dosage form to start the release at a predetermined location and/or time, and the tracking marker is located between the drug component and the delay component and comprises an indicating feature for indicating the delivery location of the drug component.

In some embodiments, the indicating feature includes whether the tracking marker can be detected in an imaging environment.

In some embodiments, the indicating feature further includes whether the tracking marker deforms in an imaging environment due to the erosion of the drug component.

In some embodiments, the indicating feature further includes whether the tracking

marker deforms in an imaging environment due to the erosion of the delay component.

In some embodiments, the indicating feature further includes whether the tracking marker deforms in an imaging environment due to the erosion of the drug component and the delay component.

In some embodiments, the imaging environment includes one or more of X-ray imaging technique, magnetic resonance imaging (MRI), ultrasound imaging, computed tomography imaging (CT), or computer image recognition technique.

In some embodiments, the tracking marker comprises a first tracking marker that is not detectable by the imaging environment after the oral drug dosage form reaches a first predetermined location and/or a first predetermined time.

In some embodiments, the tracking marker further comprises a second tracking marker that deforms after the oral drug dosage form reaches a second predetermined location and/or a second predetermined time.

In some embodiments, provided is an oral drug dosage form comprising a body, a movable component, and a tracking marker. The body comprises an expandable chamber configured to contain at least a portion of an expandable material; at least a portion of the movable component extends out of or rotates around the body by the force provided by the expandable material; the body and/or the movable component contains a drug thereon; the tracking marker is loaded in the body and/or the movable component.

In some embodiments, the tracking marker comprises a first tracking marker that is loaded onto the movable component.

In some embodiments, the tracking marker comprises a first tracking marker that is loaded in or coated on the movable component.

In some embodiments, the movable component is at least one movable arm, and the first tracking marker is located on the surface of the movable arm or at least partially embedded within the movable arm.

In some embodiments, the movable component comprises a groove in which the drug component is located.

In some embodiments, the tracking marker is located at the bottom of the groove.

In some embodiments, the drug component at least partially covers the tracking marker.

In some embodiments, the movable component is at least three movable arms, each of which carries the first tracking marker.

In some embodiments, the tracking marker comprises a second tracking marker that is c the body.

In some embodiments, the tracking marker comprises a second tracking marker that is loaded in the expandable chamber.

In some embodiments, the second tracking marker comprises a visible material admixed with the expandable material.

In some embodiments, the second tracking marker comprises a visible material not admixed with the expandable material.

In some embodiments, the expandable chamber comprises a fluid inlet for passage of a fluid, and the expandable material increases in volume upon contact with the fluid.

In some embodiments, the expandable material comprises sodium alginate (SA), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), hydroxypropyl methylcellulose (HPMC), polyethylene oxide (PEO), polyvinyl alcohol (PVA), microcrystalline cellulose (MCC), croscarmellose sodium (CCNa), carboxymethylcellulose sodium (CMC-Na), polyvinylpyrrolidone (PVPP), sodium carboxymethyl starch (CMS-Na), polyethylene glycol (PEG), or a mixture thereof.

In some embodiments, the second tracking marker expands upon imbibition of water.

In some embodiments, the present disclosure provides a method of three-dimensional printing of an oral drug dosage form, which comprises allocating materials according to a layer-by-layer model of the oral drug dosage form to print the oral drug dosage form, wherein each layer of the layer-by-layer model is allocated the following materials as needed for printing:

- (a) a non-erodible component material for forming any portion of the non-erodible component in the layer;
- (b) a pH-based enteric member material for forming any portion of the pH-based enteric member in the layer;
- (c) an erodible delay member material for forming any portion of the erodible delay member in the layer;
- (d) a drug component material for forming any portion of the drug component in the

layer; and/or

(e) a tracking marker material for forming any portion of the tracking marker in the layer.

In some embodiments, provided is a method of three-dimensional printing of an oral drug dosage form, which comprises allocating materials according to a layer-by-layer model of the oral drug dosage form to print the oral drug dosage form, wherein each layer of the layer-by-layer model is allocated the following materials as needed for printing:

(a) a pH-based enteric member material for forming any portion of the pH-based enteric member in the layer;

(b) an erodible delay member material for forming any portion of the erodible delay member in the layer;

(c) a drug component material for forming any portion of the drug component in the layer; and/or

(d) a tracking marker material for forming any portion of the tracking marker in the layer.

In some embodiments, the allocation for the drug component, the pH-based enteric member, the erodible delay member, the non-erodible component, and/or the tracking marker is performed by different print heads, respectively.

In some embodiments, the present disclosure provides a method for producing an oral drug dosage form, which is selected from three-dimensional printing, injection molding, ultrasonic welding, or any combination thereof, and then assembly is carried out to form the oral drug dosage form.

In some embodiments, the three-dimensional printing comprises allocating materials according to the layer-by-layer model of the oral drug dosage form to print the oral drug dosage form.

The present disclosure provides a method for verifying the release effect of an oral drug dosage form, which comprises:

(a) administering to an individual an oral drug dosage form having the structure according to any one of claims 1-36;

(b) imaging the individual over a time course to obtain the location and status of the

tracking marker; and

(c) determining the release condition of the drug based on the location and the status.

In some embodiments, the release condition of the drug includes whether the drug begins to be exposed to bodily fluids.

In some embodiments, the release condition of the drug further includes whether the drug has been completely released.

In some embodiments, the release condition of the drug further includes the time at which the oral drug dosage form is removed from the desired location.

In some embodiments, the desired location includes any of the following locations: stomach, duodenum, jejunum, ileum, cecum, colon, and rectum.

In some embodiments, the tracking marker is a first tracking marker, and whether the drug begins to be exposed to bodily fluids is determined based on whether the first tracking marker is detectable or the status of the first tracking marker.

In some embodiments, the status of the first tracking marker is in a pre-designed form.

In some embodiments, the tracking marker is a second tracking marker, and whether the drug has been completely released or the time at which the drug is removed from the desired location is determined based on whether the second tracking marker is detectable or the status of the second tracking marker.

In some embodiments, the time at which the drug is removed from the desired location is determined based on whether the second tracking marker is detectable.

In some embodiments, whether the drug has been completely released is determined based on the status of the second tracking marker.

In some embodiments, the status of the second tracking marker is in a pre-designed apparent deformation or an apparent deformation of the initial status of the second tracking marker.

The present disclosure provides a device for testing the release effect of an oral drug dosage form, which comprises a drug body and a tracking marker. The surface of the drug body at least partially covers the tracking marker, and the tracking marker is used for indicating the release effect of the oral drug dosage form and comprises a first tracking marker.

In some embodiments, the device further comprises a delay component that completely or partially covers the drug body.

In some embodiments, the device further comprises a non-erodible component that completely or partially covers the drug body.

In some embodiments, the delay component comprises a pH-based enteric layer for controlling the exposure of the first tracking marker and the drug body to bodily fluids in the intestinal tract.

In some embodiments, the delay component comprises a delay layer for controlling the exposure of the first tracking marker and the drug body to bodily fluids in the colon or ileum.

In some embodiments, the tracking marker comprises a second tracking marker located inside the drug body for indicating whether the drug component has been completely released.

In some embodiments, the tracking marker comprises a third tracking marker located inside the non-erodible component for indicating where the drug component is located.

In some embodiments, provided is a method for designing an oral drug dosage form configured to release a drug at a desired gastrointestinal location in an individual, which comprises:

- (a) administering to an individual an oral drug dosage form having the structure according to any one of claims 1-36;
- (b) imaging the individual over a time course to obtain the location and status of the tracking marker; and
- (c) based on the release condition of the drug determined via the location and the status of the tracking marker, adjusting the composition and proportion of the drug component, the delay or erodible component, and/or the non-erodible component to design the oral drug dosage form configured to release the drug at the desired gastrointestinal location in the individual.

In some embodiments, provided is a method for designing an oral drug dosage form configured to release a drug at a desired gastrointestinal location in an individual, which comprises:

- (a) administering to an individual an oral drug dosage form having the structure

according to any one of claims 1-36;

(b) imaging the individual over a time course to obtain the location and status of the tracking marker; and

(c) based on the release condition of the drug determined via the location and the status of the tracking marker and the plasma concentration in the individual, adjusting the composition and proportion of the drug component, the delay or erodible component, and/or the non-erodible component to design the oral drug dosage form configured to release the drug at the desired gastrointestinal location in the individual.

In some embodiments, the time course comprises a first time point and a second time point later than the first time point.

In some embodiments, one or more pharmacokinetic (PK) parameters associated with the drug are obtained after administration of the oral drug dosage form to the individual.

In some embodiments, the method further comprises identifying a relationship between the one or more PK parameters and the location and status information of the tracking marker.

In some embodiments, the method further comprises adjusting the drug component and/or the delay component or a portion thereof based on the relationship between the one or more PK parameters and the location and status information of the tracking marker.

In some embodiments, the tracking marker provided herein comprises a visible material and a high molecular polymer.

In some embodiments, the visible material comprises one or more of the following materials: bismuth potassium citrate, bismuth oxide, magnesium, magnesium alloy, titanium alloy, gold, platinum, barium sulfate, ferric sulfate, barium chloride, barium hydroxide, silver nitrate, tantalum chloride, barium tungstate, strontium tungstate, calcium tungstate, cobalt tungstate, cadmium tungstate, ferrous tungstate, tungsten carbide, tungsten oxide, tungsten boride, cerium oxide, meglumine diatrizoate, sodium diatrizoate, iodamide meglumine, meglumine iothalamate, iohexol, iopamidol, ioversol, metrizamide, gadofosveset trisodium, gadoxetic acid disodium, gadopentetate dimeglumine, gadobenate dimeglumine, gadodiamide, gadoversetamide, gadoteridol, manganese chloride, bismuth oxycarbonate ($(\text{BiO})_2\text{CO}_3$), metal powders, and metal beads.

In some embodiments, the high molecular polymer in the tracking marker may be an erodible material or a non-erodible material.

In some embodiments, the weight percentage of the visible material to the high molecular polymer in the tracking marker is 10-90:90-10, preferably 15-85:85-15, and preferably 20-80:80-20.

In some embodiments, the content of the visible material in the tracking marker accounts for 10% or more of the total material forming the tracking marker (referred to as “proportion”) as measured by the weight of the tracking marker. In some embodiments, the proportion of the visible material in the tracking marker is 20% or more. In some embodiments, the proportion of the visible material in the tracking marker is 30% or more. In some embodiments, the proportion of the visible material in the tracking marker is between 20% and 90%. In some embodiments, the proportion of the visible material in the tracking marker is between 20% and 80%. In some embodiments, the proportion of the visible material in the tracking marker is between 20% and 70%. In some embodiments, the proportion of the visible material in the tracking marker is between 30% and 90%. In some embodiments, the proportion of the visible material in the tracking marker is between 40% and 80%. In some embodiments, the proportion of the visible material in the tracking marker is between 45% and 75%.

In some embodiments, the visible material in the tracking marker is not used as a drug.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a schematic diagram of the exemplary oral drug dosage form provided herein.

FIG. 2 shows various cross sectional views of the exemplary oral drug dosage form provided herein.

FIG. 3 shows an *in vitro* dissolution profile of the exemplary oral drug dosage form provided herein. For the time points of the dissolution profile, data points are based on the mean of three replicate measurements, and the standard deviation is provided using an error bar.

FIG. 4 shows various cross sectional views of the exemplary oral drug dosage form provided herein.

FIG. 5 shows an *in vitro* dissolution profile of the exemplary oral drug dosage form provided herein. For the time points of the dissolution profile, data points are based on the mean of three replicate measurements, and the standard deviation is provided using an error bar.

FIG. 6 shows various cross sectional views of the exemplary oral drug dosage form provided herein.

FIG. 7 shows an *in vitro* accumulative dissolution profile of the exemplary oral drug dosage form provided herein. For the time points of the dissolution profile, data points are based on the mean of three replicate measurements, and the standard deviation is provided using an error bar.

FIG. 8A and **FIG. 8B** show the pharmacokinetic (PK) profiles for the reference (Xeljanz XR) and the exemplary oral drug dosage form provided herein.

FIG. 9 shows the X-ray image time course of the beagle dogs following administration of the exemplary oral drug dosage form provided herein. Annotations are provided to indicate the oral drug dosage form and to provide status information such as drug release onset and drug release completion.

FIG. 10 shows the X-ray image time course of the beagle dogs following administration of the exemplary oral drug dosage form provided herein. Annotations are provided to indicate the oral drug dosage form and to provide status information such as drug release onset and drug release completion.

FIG. 11 shows the X-ray image time course of the beagle dogs following administration of the exemplary oral drug dosage form provided herein. Annotations are provided to indicate the oral drug dosage form and to provide status information such as drug release onset and drug release completion.

FIG. 12 shows a schematic diagram of the exemplary oral drug dosage form provided herein.

FIG. 13 shows various cross sectional views of the exemplary oral drug dosage form provided herein.

FIG. 14 shows an *in vitro* accumulative dissolution profile of the exemplary oral drug dosage form provided herein.

FIG. 15 shows the pharmacokinetic (PK) profiles for the reference (Xeljanz XR) and

the exemplary oral drug dosage form provided herein in the beagle dogs.

FIG. 16A and **FIG. 16B** show the X-ray image time course of the beagle dogs following administration of the exemplary oral drug dosage form provided herein. Annotations are provided to indicate the oral drug dosage form and to provide status information such as drug release onset and drug release completion.

FIG. 17 shows the pharmacokinetic (PK) profiles for the reference (Xeljanz XR) and the exemplary oral drug dosage form provided herein.

FIG. 18 shows the X-ray image time course following administration of the exemplary oral drug dosage form provided herein. Annotations are provided to indicate the oral drug dosage form and to provide status information such as drug release onset and drug release completion.

FIG. 19A to **FIG. 19D** show the exemplary oral drug dosage form provided herein, including various angle views thereof.

FIG. 20 shows the X-ray image time course following administration of the exemplary oral drug dosage form provided herein. Annotations are provided to indicate the oral drug dosage form and to provide status information such as drug release onset.

FIG. 21A and **FIG. 21B** show schematic diagrams of the exemplary oral drug dosage form provided herein.

FIG. 22A and **FIG. 22B** show the X-ray image time course of the beagle dogs following administration of the exemplary oral drug dosage form provided herein. Annotations are provided to indicate the oral drug dosage form and to provide status information such as the retention time of the oral drug dosage form in the stomach.

FIG. 23A to **FIG. 23D** show schematic diagrams of the exemplary oral drug dosage form provided herein.

FIG. 24A to **FIG. 24C** show schematic diagrams of the exemplary oral drug dosage form provided herein.

FIG. 25 shows an *in vitro* dissolution profile of the exemplary oral drug dosage form provided herein.

FIG. 26 shows the X-ray image time course following administration of the exemplary oral drug dosage form provided herein.

FIG. 27 shows the X-ray image time course following administration of the exemplary

oral drug dosage form provided herein.

DETAILED DESCRIPTION

In the present disclosure, the delivery, release location, or release condition of the drug can be directly judged. Therefore, provided herein is an oral drug dosage form and/or method that can directly judge whether the drug is precisely located, released at a specific location, or released at a specific time in the gastrointestinal tract.

In the present disclosure, provided herein is a non-invasive way in which the number of visits is reduced and invasive methods of administration are avoided, such as injection or rectal administration.

In the present disclosure, provided herein is an improved way for designing/ validating oral drug dosage forms that provide precise drug delivery.

In some aspects, provided herein is a method for designing an oral drug dosage form configured to release a drug at a desired gastrointestinal location in an individual, which comprises: setting a tracking marker; imaging an individual; designing the drug according to the imaging location and the status of the tracking marker. In some embodiments, the oral drug dosage form has one or more tracking markers. In some embodiments, the tracking marker comprises an erodible material. In some embodiments, the tracking marker comprises a non-erodible material. In some embodiments, the tracking marker is selected from one or more of a tracking loop, a tracking strip, a tracking layer, or a tracking block. In some embodiments, the tracking marker is detected via an imaging technique. In some embodiments, the imaging is an X-ray imaging technique. In some embodiments, the imaging location is selected from one or more of the stomach, small intestine, or large intestine.

In other aspects, provided herein is an oral drug dosage form comprising a non-erodible component, a drug component, and a delay component, wherein the non-erodible component comprises a tracking marker, and/or the delay component comprises a tracking marker. In some embodiments, the non-erodible component does not comprise a tracking marker. In some embodiments, the non-erodible component comprises a tracking marker. In some embodiments, the non-erodible component comprises a tracking strip. In some embodiments, the non-erodible component comprises a tracking

loop. In some embodiments, the non-erodible component comprises a tracking layer. In some embodiments, the non-erodible component comprises two tracking loops. In some embodiments, the delay component does not comprise a tracking marker. In some embodiments, the delay component is in direct contact with a tracking marker. In some embodiments, the delay component comprises a tracking loop. In some embodiments, the drug component comprises a tracking loop or a tracking strip. In some embodiments, the drug component comprises a tracking marker material admixed with a drug.

In other aspects, provided herein is an oral drug dosage form comprising a drug component and a delay component, wherein the delay component comprises a tracking marker, and/or the drug component comprises a tracking marker. In some embodiments, the delay component does not comprise the tracking marker. In some embodiments, the delay component is in direct contact with the tracking marker. In some embodiments, the tracking marker has at least one face in contact with the delay component. In some embodiments, the top surface of the tracking marker is in contact with the bottom surface of the delay component. In some embodiments, the erosion of the tracking marker is independent of the erosion of the rest of the dosage form. In some embodiments, the tracking marker can be detected before the surface is exposed to body fluids. In some embodiments, the tracking marker cannot be detected until the surface is exposed. In some embodiments, the delay component comprises a tracking loop. In some embodiments, the drug component comprises a tracking loop or a tracking strip.

In other aspects, provided herein is an oral drug dosage form comprising a drug component and a delay component, wherein a tracking marker is located between the drug component and the delay component, and/or the drug component comprises a tracking marker. In some embodiments, the delay component does not comprise the tracking marker. In some embodiments, the delay component is in direct contact with the tracking marker. In some embodiments, the drug component comprises a tracking loop or a tracking strip. In some embodiments, the drug component comprises a tracking loop and a tracking strip.

In other aspects, provided herein is an oral drug dosage form comprising a drug component and a delay component, wherein a tracking marker is located between the drug component and the delay component, and/or the drug component comprises a tracking marker. In some embodiments, the delay component does not comprise the

tracking marker. In some embodiments, the delay component is in direct contact with the tracking marker. In some embodiments, the drug component comprises a tracking loop or a tracking strip. In some embodiments, the drug component comprises a tracking loop and a tracking strip.

The oral drug dosage form described herein is based on the unique insight and discovery by the inventors of the design and manufacture of oral drug dosage forms for precisely targeted drug delivery in the gastrointestinal tract. As illustrative examples of the utility of such oral drug dosage forms provided herein, certain conditions affect specific regions of the gastrointestinal tract, such as ulcerative colitis causing inflammation and ulceration in the innermost lining of the large intestine (colon) and rectum. Known agents, such as anti-inflammatory agents including JAK inhibitors (e.g., tofacitinib), are effective in treating individuals having ulcerative colitis by reducing inflammation and ulcer formation. However, certain agents can cause unacceptable levels of toxicity, thereby limiting the use, efficacy, and patient compliance of such agents. Therefore, it is particularly important to precisely locate the drug release site. Targeted drug delivery using the oral drug dosage form provided herein can improve efficacy by delivering the drug to the desired location of action (e.g., at or near the colon of an individual), while also reducing adverse events associated with systemic toxicity.

In other aspects, provided herein is an oral drug dosage form comprising a body comprising an expandable member located within a chamber; two or more movable components comprising a tracking marker; a drug component located at the body and/or the movable component; the expandable member comprises a tracking marker. The oral drug dosage form is configured with a pre-administration status in a compact form and a post-administration status in an unfolded form that provides gastric retention. In some embodiments, the expandable material is admixed with a tracking marker material. In some embodiments, the two or more movable components rotate on separate shafts in a direction perpendicular to the plane of the original location. In some embodiments, the two or more movable components rotate in opposite directions on the same shaft.

The disclosure provided herein also encompasses oral drug dosage forms that do not have one or more tracking markers. For example, these tracking markers may not be needed after the development and optimization of an oral drug dosage form.

In other aspects, provided herein is a method of three-dimensional printing of an oral drug dosage form, which comprises allocating materials according to a layer-by-layer

model of the oral drug dosage form to print the oral drug dosage form, wherein each layer of the layer-by-layer model is allocated the following materials as needed for printing: (a) a non-erodible component material for forming any portion of the delay component in the layer; (b) a pH-based enteric member material for forming any portion of the pH-based enteric member in the layer; (c) an erodible delay member material for forming any portion of the erodible delay member in the layer; (d) a drug component material for forming any portion of the drug component in the layer; and/or (e) a tracking marker material for forming any portion of the tracking marker in the layer.

In other aspects, provided herein is a method of three-dimensional printing of an oral drug dosage form, which comprises allocating materials according to a layer-by-layer model of the oral drug dosage form to print the oral drug dosage form, wherein each layer of the layer-by-layer model is allocated the following materials as needed for printing: (a) a pH-based enteric member material for forming any portion of the pH-based enteric member in the layer; (b) an erodible delay member material for forming any portion of the erodible delay member in the layer; (c) a drug component material for forming any portion of the drug component in the layer; and/or (d) a tracking marker material for forming any portion of the tracking marker in the layer.

In other aspects, provided herein is a method of three-dimensional printing of an oral drug dosage form, which is selected from three-dimensional printing, injection molding, ultrasonic welding, or any combination thereof for production, and then assembly is carried out to form a pre-administration oral drug dosage form; the body (or one or more portions thereof) is produced independently of each movable arm, and these components are then assembled to form an oral drug dosage form. In some embodiments, the three-dimensional printing comprises allocating materials according to the layer-by-layer model of the oral drug dosage form to print the oral drug dosage form, and the allocation is performed via hot melt extrusion deposition (MED).

In other aspects, provided herein is a method for verifying the release effect of an oral drug dosage form comprising a tracking marker and a drug component, and the method comprises: (a) administering a drug; (b) imaging to obtain the location and status of the tracking marker; (c) determining the drug release condition based on the location and the status. In some embodiments, the imaging is an X-ray imaging technique. In some embodiments, the location of the tracking marker is selected from one or more of the stomach, small intestine, or large intestine. In some embodiments, the status of the

tracking marker is selected from one or more of complete, incomplete, distorted shape, lightened image, and disappearing image. In some embodiments, the status of the tracking marker is determined based on the angle between the tracking markers and/or relative position of the tracking markers. In some embodiments, the location where the drug begins to release and the location where the drug is completely released can be precisely located by the method for verifying the release effect of an oral drug dosage form provided herein. In some embodiments, the retention time of the drug in the stomach can be accurately determined by the method for verifying the release effect of an oral drug dosage form provided herein.

In other aspects, provided herein is a device for testing the release effect of an oral drug dosage form, which comprises a non-erodible component, a delay component, a first tracking marker, and/or a second tracking marker, wherein whether the drug achieves a preset release effect or not is determined according to the imaging locations and status of the first tracking marker and the second tracking marker.

In other aspects, provided herein is a device for testing the release effect of an oral drug dosage form, which comprises a delay component, a first tracking marker, and/or a second tracking marker, wherein whether the drug achieves a preset release effect or not is determined according to the imaging locations and status of the first tracking marker and the second tracking marker.

In other aspects, provided herein is a device for testing the release effect of an oral drug dosage form, which comprises a body, a movable component, a first tracking marker, and/or a second tracking marker, wherein whether the drug achieves a preset release effect or not is determined according to the imaging locations and status of the first tracking marker and the second tracking marker.

The device for testing the release effect of an oral drug dosage form provided herein can be used to test any oral drug dosage form that requires targeted drug delivery or site-specific retention time. In some embodiments, the oral drug dosage form that is located at or near the colon of an individual is tested. In some embodiments, the oral drug dosage form that is located at the stomach is tested. In some embodiments, the oral drug dosage form is tested for gastric retention time.

In other aspects, provided herein is a device for testing the erosion effect of a delay component comprised in an oral drug dosage form, comprising a compartment formed

by a first erodible material; a delay component comprising the first erodible material, wherein the delay component covers the compartment, and a first tracking marker comprising: a second erodible material admixed with a first visible material, wherein the first tracking marker is embedded in the delay component. In some embodiments, the status of the first tracking marker which deforms or disappears indicate the erosion effect of the delay component. In some embodiments, at least one face of the first tracking marker is in contact with the compartment. In some embodiments, the deformation of the first tracking marker indicates the beginning of the erosion of the delay component. In some embodiments, the disappearance of the first tracking marker indicates the ending of the erosion of the delay component. In some embodiments, the compartment is empty which is configured to contain a drug or a drug component. In some embodiments, the compartment comprises a drug component comprising a third erodible material admixed with a drug. In some embodiments, the compartment comprises a second tracking marker comprising a fourth erodible material admixed with a second visible material.

Definitions of Terms

For the purpose of illustrating the present specification, the following definitions will be applied. In case any of the definitions set forth below conflict with any document incorporated herein by reference, the definitions set forth below shall control.

As used herein, the use of the term “treatment” or its equivalent refers to a method for obtaining a beneficial or desired result, including alleviation of symptoms of, for example, a disease. For purposes of the present disclosure, beneficial or desired clinical results include, but are not limited to, one or more of the following: relieving one or more symptoms caused by a disease, reducing the severity of one or more symptoms caused by a disease, preventing an increase in the severity of one or more symptoms caused by a disease, reducing the dosage of one or more other drugs required to treat and/or control a disease, and improving the quality of life.

As used herein, the term “individual” refers to mammals and includes, but is not limited to, humans, cows, horses, cats, dogs, rodents, rats, mice, dogs, or primates. In some embodiments, the individual is a human individual.

As used herein, the terms “comprising”, “having”, “containing”, and “including”, as well as other similar forms and grammatical equivalents thereof, are intended to be equivalent in meaning and be open-ended, i.e., one or more items following any of these words are not meant to be an exhaustive listing of the one or more items, nor are they meant to be limited to only the listed one or more items. For example, an article of manufacture “comprising” components A, B, and C may consist of components A, B, and C (i.e., containing only components A, B, and C), or may comprise not only components A, B, and C, but also one or more other components. Thus, it is intended that “comprising” and its similar forms, as well as grammatical equivalents thereof, include disclosure of an embodiment “consisting essentially of...” or “consisting of...”.

It should be understood that when a range of values is provided, every intermediate value (to the tenth of the unit of the lower limit) between the upper and lower limit of that range and any other stated or intermediate values in that stated range are encompassed within the present disclosure and subject to any specifically excluded limit in the stated range unless the context clearly dictates otherwise. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the present disclosure.

Reference herein to an “about” value or parameter includes (and describes) variations that are directed to that value or parameter itself. For example, a description referring to “about X” includes a description of “X”. Exemplary degrees of error encompassed with use of the term about are within 20 percent (%), such as within 15%, within 10%, or within 5% of a given value or range of values.

As used herein, the use of the term “a shape of a capsule” or its equivalent refers to an elongated shape comprising two parallel lines and two arcs, wherein the two parallel lines are connected by the two arcs viewing from the front and comprising a circle viewing from a plane perpendicular.

As used herein, including the appended claims, the singular forms “a”, “or”, and “the” include plural referents unless the context clearly dictates otherwise.

As used herein, the use of the term “tracking strip” or its equivalent refers to a tracking marker in the form of a strip and does not represent a limitation on its length or thickness.

As used herein, the use of the term “tracking layer” or its equivalent refers to a tracking marker unfolding planarly and does not represent a limitation on its thickness or length. In some embodiments, a tracking layer may comprise many printed layers, such as printed via additive manufacturing, e.g., 3D printing, forming the tracking layer.

As used herein, the use of the term “a tracking marker deforms” or its equivalent refers to a twisted shape, an incomplete shape, or other shapes which are changed a little from the original shape of a tracking marker.

I. Method for designing oral drug dosage form

Provided herein is a method for designing an oral drug dosage form configured to release a drug at a desired gastrointestinal location in an individual, which comprises setting a tracking marker, imaging an individual, and designing the drug according to the imaging location and the status of the tracking marker. In some embodiments, the oral drug dosage form has one or more tracking markers. In some embodiments, the tracking marker comprises an erodible material. In some embodiments, the tracking marker comprises a non-erodible material. In some embodiments, the tracking marker is selected from one or more of a tracking loop, a tracking strip, a tracking layer, or a tracking block. In some embodiments, the shape of the tracking layer or the cross-sectional shape of the tracking block is selected from one or more of a circle, a triangle, a quadrangle, a pentagon, and a hexagon. In some embodiments, the tracking marker is detected via an imaging technique.

In some embodiments, the imaging can be done as a number of separate occurrences to monitor for location and status of the tracking marker.

In some embodiments, the imaging can be a continuous imaging.

In some embodiments, the imaging is selected from one or more of X-ray imaging technique, magnetic resonance imaging (MRI), ultrasound imaging, computed tomography imaging (CT), or computer image recognition technique. In some embodiments, the imaging is an X-ray imaging technique.

In some embodiments, releasing the drug at the desired gastrointestinal location comprises releasing the drug at, near, or downstream of the ileum (such as at any one or more of the cecum, ascending colon, transverse colon, descending colon, and/or sigmoid colon) of the individual. In some embodiments, releasing the drug at the

desired gastrointestinal location described herein comprises releasing the drug in the stomach. In some embodiments, releasing the drug at the desired gastrointestinal location described herein comprises releasing the drug during the gastric retention. In some embodiments, releasing the drug at the desired gastrointestinal location described herein is releasing the drug at or near the colon of the individual.

In some embodiments, the imaging location is selected from one or more of the stomach, small intestine, or large intestine. In some embodiments, the imaging location is in the stomach of the individual. In some embodiments, the imaging location is at or near the colon of the individual.

In some embodiments, the status of the tracking marker is selected from one or more of complete, reduced size, incomplete, distorted shape, lightened image, and disappearing image. In some embodiments, the time at which the tracking marker of each component changes from a complete status to another status (e.g., reduced size, incomplete, distorted shape, and lightened or disappearing image) is taken as the time at which each component begins to erode. For example, in some embodiments, the time at which the tracking marker in the drug component changes from a complete status to a lightened image status is taken as the time at which drug release begins. In some embodiments, the time at which the tracking marker in the drug component changes to a disappearing status is taken as the time at which drug release is completed.

Designing the drug described herein allows for the determination of the start and end times of drug release by observing the status of the tracking marker, so that the duration of the drug release and the drug release location can be determined, truly achieving controllable drug release.

In some embodiments, the status of the tracking marker is determined based on the angle between the tracking markers. In some embodiments, the status of the tracking marker is determined based on a relative position between the tracking markers. In some embodiments, the status of the tracking marker is determined based on the number of the tracking marker.

Designing the drug described herein allows for the determination of the position of the movable component or the body by observing the status, the angle, or the number of the tracking marker, realizing the visualization of the drug transfer process and the accurate control of the retention time. In cases when the drug component fully or

partially covers the tracking marker, the deformations or disappearance of the tracking marker can indicate the end time of the drug release.

Designing the drug described herein allows for the adjustment in the oral drug dosage form for releasing the drug at the desired gastrointestinal location by one or more means selected from the adjustments in the size of each member (e.g., the thickness and the surface area of each member) and the compositions of each member (e.g., the type and the content of each component) of the oral drug dosage form. In some embodiments, if the location where the drug begins to release and/or the location where the drug is completely released, as determined by the imaging location and status of the tracking marker, is later than the desired gastrointestinal location, the oral drug dosage form can be adjusted to release the drug at the desired gastrointestinal location by one or more means of adjusting the size of each member (e.g., decreasing the thickness of the delay component and/or increasing the surface area of the delay component) and the compositions of each member (e.g., using a second erodible material with a high erosion rate or increasing its content in the delay component, and/or using a first erodible material with a high erosion rate or increasing its content in the drug component) of the oral drug dosage form. In some embodiments, if the location where the drug begins to release and/or the location where the drug is completely released, as determined by the imaging location and status of the tracking marker, is earlier than the desired gastrointestinal location, the oral drug dosage form can be adjusted to release the drug at the desired gastrointestinal location by one or more means of adjusting the size of each member (e.g., increasing the thickness of the delay component and/or decreasing the surface area of the delay component) and the compositions of each member (e.g., using a second erodible material with a low erosion rate or increasing its content in the delay component, and/or using a first erodible material with a low erosion rate or increasing its content in the drug component) of the oral drug dosage form.

In some embodiments, if the retention time of the oral drug dosage form is shorter than the desired one, the oral drug dosage form can be adjusted to stay for a longer time by one or more means of adjusting the size of each component and/or the body (e.g., increasing the length of the movable component, increasing the width of the movable component, and/or increasing the volume of the body), and the compositions of each component and/or the body (e.g., using a material comprised in the movable component with high mechanical strength and/or high elasticity, using the expandable material with

longer-lasting swelling properties) of the oral drug dosage form.

In some embodiments, if the retention time of the oral drug dosage form is longer than the desired one, the oral drug dosage form can be adjusted to stay for a shorter time by one or more means of adjusting the size of each component and/or the body (e.g., decreasing the length of the movable component, decreasing the width of the movable component, and/or decreasing the volume of the body), and the compositions of each component and/or the body (e.g., using a material comprised in the movable component with low mechanical strength and/or low elasticity, using the expandable material with shorter-lasting swelling properties) of the oral drug dosage form.

In some embodiments, designing the drug described herein further comprises designing an oral drug dosage form with artificial intelligence (AI) to release the drug at a desired gastrointestinal location based on the imaging location and the tracking marker status.

In some embodiments, designing the drug described herein further comprises designing an oral drug dosage form with artificial intelligence (AI) to achieve retention of the drug in the stomach for a desired time based on the imaging location and the tracking marker status.

II. Oral drug dosage form

In some aspects, provided herein is an oral drug dosage form comprising: a drug component comprising a first erodible material admixed with a drug and a first erodible tracking marker; a non-erodible component; a delay component that is not admixed with the drug and comprises a pH-based enteric member configured to erode at or above a predetermined pH value; and an erodible delay member comprising a second erodible material. The pH-based enteric member prevents the erosion of the erodible delay member, and the erodible delay member prevents the erosion of the drug component.

In some embodiments, the non-erodible component comprises a second tracking marker, and the imaging is further used to obtain the status of the second tracking marker. In some embodiments, the pH-based enteric member comprises a third tracking marker, and the imaging is further used to obtain the status of the third erodible tracking marker. In some embodiments, the erodible delay member comprises a fourth tracking marker, and the imaging is further used to obtain the status of the fourth erodible

tracking marker.

In other aspects, provided herein is an oral drug dosage form comprising: a drug component comprising a first erodible material admixed with a drug and a first erodible tracking marker; and a delay component that is not admixed with the drug and comprises a second erodible material. The delay component prevents the erosion of the drug component.

In some embodiments, the delay component comprises a second tracking marker, and the imaging is further used to obtain the status of the second erodible tracking marker. In some embodiments, the drug component comprises a first erodible tracking loop and a first erodible tracking strip. In some embodiments, one face of the first erodible tracking loop is in direct contact with the delay component. In some embodiments, the drug component completely or partially surrounds the first erodible tracking strip.

In other aspects, provided herein is an oral drug dosage form comprising: a drug component comprising a first erodible material admixed with a drug and a first erodible tracking marker; a delay component that is not admixed with the drug and comprises a pH-based enteric member configured to erode at or above a predetermined pH value; and an erodible delay member comprising a second erodible material. The pH-based enteric member prevents the erosion of the erodible delay member, and the erodible delay member prevents the erosion of the drug component.

In some embodiments, the pH-based enteric member comprises a second tracking marker, and the imaging is further used to obtain the status of the second erodible tracking marker. In some embodiments, the erodible delay member comprises a third tracking marker, and the imaging is further used to obtain the status of the third erodible tracking marker.

In other aspects, provided herein is an oral drug dosage form comprising: a body comprising an expandable member located within a chamber; two or more movable components comprising two or more tracking markers; a drug component located at the body and/or the movable component.

In some embodiments, the body comprises a tracking marker, and the imaging is further used to obtain the status of the tracking marker. In some embodiments, the chamber of the body comprises a tracking marker, and the imaging is further used to obtain the status of the tracking marker.

In some embodiments, the tracking marker may be a single or composite composition of a tracking loop, a tracking strip, a tracking layer, and a tracking block.

In some embodiments, the oral drug dosage form has any shape. In some embodiments, the oral drug dosage form has a shape of a capsule, a cylinder, an elliptic cylinder, or a combination thereof.

In some embodiments, the surface of the non-erodible component has any shape. In some embodiments, the surface of the non-erodible component has a shape of a circle, an ellipse, a bullet, an arrow, a triangle, an arc triangle, a square, an arc square, a rectangle, an arc rectangle, a diamond, a pentagon, a hexagon, an octagon, a half-moon, an almond, or a combination thereof.

In some embodiments, the non-erodible component comprises a thermoplastic material, such as a thermoplastic polymer. In some embodiments, the non-erodible component comprises a material comprising any one or more of a matrix material, a plasticizer, or other additives (e.g., fillers, binders, lubricants, glidants, and disintegrants).

In some embodiments, the matrix material comprises any one or more of copovidone, polyvinylpyrrolidone-co-vinyl acetate, polyvinylpyrrolidone-polyvinyl acetate copolymer, crospovidone, polyvinylpyrrolidone, hydroxypropyl cellulose, hypromellose, hydroxypropyl methylcellulose phthalate, methylcellulose, methacrylic acid copolymer, poly(methacrylic acid-co-ethyl acrylate), poly(butyl methacrylate-co-(2-dimethylaminoethyl)methacrylate-co-methyl methacrylate) 1:2:1, poly(dimethylaminoethyl methacrylate-co-methacrylate), poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonium ethyl methacrylate chloride), poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1, poly(methacrylic acid-co-methyl methacrylate) 1:2, poly(methacrylic acid-co-ethyl acrylate) 1:1, poly(methacrylic acid-co-methyl methacrylate) 1:1, polyethylene oxide, polyethylene glycol, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer 57/30/13, polyethylene glycol-polyvinyl alcohol graft copolymer 25/75, Kollicoat IR-polyvinyl alcohol 60/40, polyvinyl alcohol, aminoalkyl methacrylate copolymer E, hydroxypropyl methylcellulose acetate succinate or hypromellose acetate succinate, methacrylate copolymer, ammonio alkyl methacrylate copolymer, ethylcellulose, polyvinyl acetate, polyvinylpyrrolidone 80/20, polyvinylacetal diethylamino lactate, maltitol, lactose monohydrate, xylitol, isomalt, sucrose, glucose, dextran 70, or maltose.

In some embodiments, the plasticizer is any one or more of triethyl citrate, vitamin E polyethylene glycol succinate, acetylated triethyl citrate, tributyl citrate, tributyl *o*-acetyl citrate, polyethylene glycol 15-hydroxystearate, PEG-40 hydrogenated castor oil, polyethylene glycol 35-castor oil, dibutyl sebacate, diethyl phthalate, glycerin, methyl 4-hydroxybenzoate, castor oil, oleic acid, glyceryl triacetate, polyalkylene glycol, stearic acid, palmitic acid, malic acid, polyethylene glycol, lauroyl PEG-32 glyceride, poloxamer 188, poloxamer 407, acetyl tributyl citrate, D-sorbitol, propylene glycol, citric acid, glyceryl behenate, D-mannitol, polysorbate, sorbitan monostearate, sorbitan monooleate, or polyoxyethylene 40 stearate.

In some embodiments, the other additives are any one or more of acacia, alginate, alginic acid, aluminum acetate, butyl paraben, butylated hydroxytoluene, citric acid, calcium carbonate, candelilla wax, croscarmellose sodium, powdered sugar, colloidal silica, cellulose, ordinary or anhydrous calcium phosphate, carnauba wax, corn starch, carboxymethylcellulose calcium, calcium disodium ethylenediaminetetraacetate, dehydrated dicalcium phosphate, cetylpyridinium chloride, dibasic calcium phosphate, tribasic calcium phosphate, bibasic calcium phosphate, disodium hydrogen phosphate, polydimethylsiloxane, sodium tetraiodofluorescein, ethylenediaminetetraacetic acid, gelatin, glycerol monooleate, ferroferric oxide, ferric oxide, yellow iron oxide, red iron oxide, lactose (aqueous, anhydrous, monohydrate, or spray dried), microcrystalline cellulose, magnesium carbonate, magnesium oxide, methyl paraben, polysorbate 80, propyl paraben, potassium bicarbonate, potassium sorbate, potato starch, phosphoric acid, polyoxyethylene (40) stearate, sodium starch glycolate, pregelatinized starch, croscarmellose sodium, sodium lauryl sulfate, starch, silicon dioxide, sodium benzoate, sucrose, sorbic acid, sodium carbonate, sodium saccharin, sodium alginate, silica gel, sorbitan monooleate, sodium chloride, sodium metabisulfite, dehydrated sodium citrate, sodium starch, sodium carboxymethylcellulose, succinic acid, sodium propionate, titanium dioxide, or talc.

The oral drug dosage form provided herein comprises a delay component, which comprises an erodible material, such as an erodible material different from a drug component. Typically, the drug component is located in the oral drug dosage form such that the drug component is not affected by bodily fluids after administration to the individual, prior to erosion (such as substantially complete erosion) of the delay component. In some embodiments, the delay component described herein is a delay

component layer. In some embodiments, the delay component comprises more than one layer of erodible material, such as two layers of erodible material. In some embodiments, the delay component does not comprise a drug.

The delay component described herein comprises a pH-based enteric member, such as a pH-based enteric member layer. In some embodiments, the pH-based enteric member comprises more than one layer of pH-based enteric material, such as two layers of pH-based enteric material. In some embodiments, the pH-based enteric member does not comprise a drug.

The pH-based enteric member is configured to erode at or above a desired pH. As understood in the art, different regions of the human gastrointestinal tract have environments with different pH. The use of such pH-based enteric members helps to control erosion of the component of the oral drug dosage form described herein to the desired location in the gastrointestinal tract. In some embodiments, the pH-based enteric member erodes at a pH value of about 5.5 to about 8, such as any one of about 5.5 to about 7.5 and about 6 to about 7. In some embodiments, the pH-based enteric member erodes at or above a pH value of about 5.5, such as any one of about 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, or 8.

A variety of materials having different shapes and sizes may be used to form the pH-based enteric member. In some embodiments, the pH-based enteric member is a layer of pH-based enteric material. In some embodiments, the pH-based enteric member is configured with a surface, such as a surface exposed to bodily fluids during the administration of the oral drug dosage form to a human individual, and the surface has a predetermined shape and surface area. For example, in some embodiments, the pH-based enteric member has a top surface and a bottom surface, wherein the top surface is exposed to bodily fluids prior to the bottom surface. In some embodiments, the pH-based enteric member is a layer having a top surface and a bottom surface. In some embodiments, the top surface of the pH-based enteric member is not flat, e.g., includes certain feature parts that extend beyond the top surface plane or surface tolerance threshold (as measured between two parallel planes), such as to reduce adhesion of the pH-based enteric member or a portion thereof to an internal body part of a human individual. In some embodiments, the top surface of the pH-based enteric member or at least a portion thereof is flat or within the surface tolerance threshold.

The surface of the pH-based enteric member (such as a pH-based enteric layer) may have any shape, such as based on the surface exposed to bodily fluids upon administration. In some embodiments, the surface has a shape of a capsule, a circle, an ellipse, a bullet, an arrow, a triangle, an arc triangle, a square, an arc square, a rectangle, an arc rectangle, a diamond, a pentagon, a hexagon, an octagon, a half-moon, an almond, or a combination thereof.

In some embodiments, the surface area of the bodily fluid-exposed surface of the pH-based enteric member is uniform throughout the thickness of the pH-based enteric member. For example, as the pH-based enteric member erodes, the surface exposed to bodily fluids has the same surface area. In some embodiments, the surface area of the bodily fluid-exposed surface of the pH-based enteric member is different at two or more points. For example, as the pH-based enteric member erodes, the surface exposed to bodily fluids changes, such as the surface area increases and/or decreases during the erosion of the pH-based enteric member. In some embodiments, the shape of the bodily fluid-exposed surface of the pH-based enteric member is uniform throughout the thickness of the pH-based enteric member. In some embodiments, the shape of the bodily fluid-exposed surface of the pH-based enteric member is different at two or more points.

In some embodiments, the pH-based enteric member layer comprises a top surface and a bottom surface, and the thickness (as measured between the top surface and the bottom surface) is substantially uniform, such as within 20% of the average thickness.

In some embodiments, the pH-based enteric member (such as the pH-based enteric layer) comprises a thermoplastic material, such as a thermoplastic polymer. In some embodiments, the pH-based enteric member (such as the pH-based enteric layer) comprises a material comprising any one or more of a matrix material, a plasticizer, or other additives (e.g., fillers, binders, lubricants, glidants, and disintegrants).

The oral drug dosage form provided herein comprises an erodible delay member, which comprises an erodible material, such as an erodible material different from a drug component. Typically, the erodible delay member is located in the oral drug dosage form such that the erodible delay member is not affected by bodily fluids after administration to the individual, prior to erosion (such as substantially complete erosion) of the pH-based enteric member. In some embodiments, the delay component described herein comprises an erodible delay member, such as an erodible delay

member layer. In some embodiments, the erodible delay member comprises more than one layer of erodible delay material, such as two layers of erodible delay material. In some embodiments, the erodible delay member does not comprise a JAK inhibitor.

The erodible delay member is configured to erode within a predetermined amount of time after exposure to bodily fluids, such as after erosion (such as substantially complete erosion) of the pH-based enteric member or layer thereof. In some embodiments, the erodible delay member erodes (such as substantially completely erodes) over a period from about 1 min to about 7 h to expose another component of the oral drug dosage form. In some embodiments, the erodible delay member erodes (such as substantially completely erodes) over a period of at least about 5 min, such as any one of at least about 10 min, 20 min, 30 min, 40 min, 50 min, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 5.5 h, 6 h, 6.5 h, or 7 h, to expose another component of the oral drug dosage form. The time for erosion of the erodible delay member or layer thereof may be based on a number of factors including composition and thickness.

The erodible delay member may be formed using a variety of materials having different shapes and sizes. In some embodiments, the erodible delay member is a layer of erodible delay material. In some embodiments, the erodible delay member is configured with a surface, such as a surface exposed to bodily fluids during the administration of the oral drug dosage form to a human individual, and the surface has a predetermined shape and surface area. For example, in some embodiments, the erodible delay member has a top surface and a bottom surface, wherein the top surface is exposed to bodily fluids prior to the bottom surface. In some embodiments, the erodible delay member is a layer having a top surface and a bottom surface. In some embodiments, the top surface of the erodible delay member is not flat, e.g., includes certain feature parts that extend beyond the top surface plane or surface tolerance threshold (as measured between two parallel planes). In some embodiments, the top surface of the erodible delay member or at least a portion thereof is flat or within the surface tolerance threshold.

The surface of the erodible delay member (such as the erodible delay member layer) may have any shape, such as based on the surface exposed to bodily fluids upon administration. In some embodiments, the surface has a shape of a capsule, a circle, an ellipse, a bullet, an arrow, a triangle, an arc triangle, a square, an arc square, a rectangle, an arc rectangle, a diamond, a pentagon, a hexagon, an octagon, a half-moon, an almond, or a combination thereof.

In some embodiments, the surface area of the bodily fluid-exposed surface of the erodible delay member is uniform throughout the thickness of the erodible delay member. For example, as the erodible delay member erodes, the surface exposed to bodily fluids has the same surface area. In some embodiments, the surface area of the bodily fluid-exposed surface of the erodible delay member is different at two or more points. For example, as the erodible delay member erodes, the surface exposed to bodily fluids changes, such as the surface area increases and/or decreases during the erosion of the erodible delay member. In some embodiments, the shape of the bodily fluid-exposed surface of the erodible delay member is uniform throughout the thickness of the erodible delay member. In some embodiments, the shape of the bodily fluid-exposed surface of the erodible delay member is different at two or more points.

In some embodiments, the erodible delay member layer comprises a top surface and a bottom surface, and the thickness (as measured between the top surface and the bottom surface) is substantially uniform, such as within 20% of the average thickness.

In some embodiments, the erodible delay member (such as the erodible delay member layer) comprises a thermoplastic material, such as a thermoplastic polymer. In some embodiments, the erodible delay member (such as the erodible delay member layer) comprises a material comprising any one or more of a matrix material, a plasticizer, or other additives (e.g., fillers, binders, lubricants, glidants, and disintegrants).

In other aspects, provided herein is an oral drug dosage form comprising: a body comprising an expandable member located within a chamber; a movable component comprising a tracking marker; a drug component located at the body and/or the movable component. The movable component or a portion thereof is configured to slide within a directional channel such that the movable component extends beyond or away from the body of the oral drug dosage form along an axis based on the directional channel.

In some embodiments, the oral drug dosage form comprises: a body comprising an expandable member located within a chamber; a movable component comprising a groove; a tracking marker located within the groove; a drug component located within the groove. The movable component or a portion thereof is configured to slide within a directional channel such that the movable component extends beyond or away from the body of the oral drug dosage form along an axis based on the directional channel.

In some embodiments, the tracking marker is located at the bottom of the groove. In

some embodiments, the drug component is located on the tracking marker. In some embodiments, the drug component at least partially covers the tracking marker.

In some embodiments, the oral drug dosage form comprises an expandable member; the movable component is configured such that at least a portion of the movable component extends to or rotates around the body of the oral drug dosage form by the force provided by the expandable member, and the movable component comprises a tracking marker; the body comprises a chamber configured to comprise at least a portion of the expandable member, wherein the chamber operably comprises one or more fluid inlets; a directional channel and an orifice operably connected to the chamber, wherein the movable component comprises a contact component configured to contact the expandable member or a feature associated with the expandable member near the directional channel and the orifice; a drug, wherein the oral drug dosage form is configured with a pre-administration status in a compact form and a post-administration status in an unfolded form that provides gastric retention, and the post-administration status in the unfolded form of the oral drug dosage form is at least partially due to the expansion of the expandable member in the presence of gastrointestinal fluid.

In some embodiments, the oral drug dosage form comprises: an expandable member; a movable component configured such that at least a portion of the movable component can extend out of or further away from a body of the oral drug dosage form by a force provided by the expandable member; the body comprising a chamber configured to comprise at least a portion of the expandable member; a directional channel operably connected to the chamber, wherein the movable component comprises a contact component configured to contact the expandable member near the directional channel, the chamber and the contact component of the movable component substantially surround the expandable member, the movable component or a portion thereof is configured to slide within the directional channel such that the movable component extends out of or further away from the body of the oral drug dosage form along a shaft based on the directional channel, and the movable component comprises a tracking marker; one or more fluid inlets operably connected to the chamber; a stopper configured to engage the movable component in an extended position; and a drug. The oral drug dosage form is configured with a pre-administration status in a compact form and a post-administration status in an unfolded form that provides gastric retention, and

the post-administration status in the unfolded form of the oral drug dosage form is at least partially due to the expansion of the expandable member in the presence of gastrointestinal fluid.

In some embodiments, the oral drug dosage form comprises: an expandable member; a first movable component and a second movable component, wherein the first movable component and the second movable component are configured such that at least a portion of each movable component can extend out of or further away from a body of the oral drug dosage form by a force provided by the expandable member, the first movable component and the second movable component extend in substantially opposite directions along a shaft based on a directional channel, and the movable component comprises a tracking marker; the body comprising a chamber configured to comprise at least a portion of the expandable member; a first directional channel and a second directional channel operably connected to the chamber, wherein the first movable component comprises a first contact component configured to contact the expandable member near the first directional channel, the second movable component comprises a second contact component configured to contact the expandable member near the second directional channel, the chamber, the first contact component of the first movable component, and the second contact component of the second movable component substantially surround the expandable member, the first movable component or a portion thereof is configured to slide within the first directional channel such that the first movable component extends out of or further away from the body of the oral drug dosage form along the axis, and the second movable component or a portion thereof is configured to slide within the second directional channel such that the second movable component extends out of or further away from the body of the oral drug dosage form along the axis; one or more fluid inlets operably connected to the chamber; a first stopper configured to engage the first movable component in an extended position; a second stopper configured to engage the second movable component in the extended position; and a drug. The oral drug dosage form is configured with a pre-administration status in a compact form and a post-administration status in an unfolded form that provides gastric retention, and the post-administration status in the unfolded form of the oral drug dosage form is at least partially due to the expansion of the expandable member in the presence of gastrointestinal fluid.

Provided is an oral drug dosage form for gastric retention. The oral drug dosage form

comprises: a first expandable member; a first movable component, wherein the first movable component is configured such that at least a portion of the movable component can extend out of or further away from a body of the oral drug dosage form by a force provided by the first expandable member, and the first movable component is configured to rotate around a first shaft; a second expandable member; a second movable component, wherein the second movable component is configured such that at least a portion of the movable component can extend out of or further away from the body of the oral drug dosage form by a force provided by the second expandable member, the second movable component is configured to rotate on a second shaft, and the movable component comprises a tracking marker; the body comprising a first chamber configured to comprise at least a portion of the first expandable member; a first directional channel operably connected to the first chamber, wherein the first directional channel comprises a curved channel, the first movable component comprises a first contact component configured to contact the first expandable member near the first directional channel, the first chamber and the first contact component of the first movable component substantially surround the first expandable member, the first movable component or a portion thereof is configured to rotate on the first shaft by the first contact component sliding on the first directional channel such that the first movable component extends out of or further away from the body of the oral drug dosage form, and one or more fluid inlets are operably connected to the first chamber; a second chamber configured to comprise at least a portion of the second expandable member; a second directional channel operably connected to the second chamber, wherein the second directional channel comprises a curved channel, the second movable component comprises a second contact component configured to contact the second expandable member near the second directional channel, the second chamber and the second contact component of the second movable component substantially surround the second expandable member, the second movable component or a portion thereof is configured to rotate on the second shaft by the second contact component sliding on the second directional channel such that the second movable component extends out of or further away from the body of the oral drug dosage form, and the one or more fluid inlets are operably connected to the second chamber; and a drug. The oral drug dosage form is configured with a pre-administration status in a compact form and a post-administration status in an unfolded form that provides gastric retention, and the

post-administration status in the unfolded form of the oral drug dosage form is at least partially due to the expansion of the expandable member in the presence of gastrointestinal fluid.

Provided is an oral drug dosage form for gastric retention. The oral drug dosage form comprises: a first expandable member; a first movable component and a second movable component, wherein the first movable component and the second movable component are configured such that at least a portion of each movable component can extend out of or further away from a body of the oral drug dosage form by a force provided by the first expandable member, and the first movable component and the second movable component extend in substantially opposite directions along a shaft based on a directional channel; a second expandable member; a third movable component, wherein the third movable component is configured such that at least a portion of the third movable component can extend out of or further away from the body of the oral drug dosage form by a force provided by the second expandable member, and the third movable component is configured to rotate on a first shaft; a third expandable member; a fourth movable component, wherein the fourth movable component is configured such that at least a portion of the fourth movable component can extend out of or further away from the body of the oral drug dosage form by a force provided by the third expandable member, the fourth movable component is configured to rotate on a second shaft, and the movable component comprises a tracking marker; the body comprising a first chamber configured to comprise at least a portion of the first expandable member; a first directional channel and a second directional channel operably connected to the first chamber, wherein the first movable component comprises a first contact component configured to contact the first expandable member near the first directional channel, the second movable component comprises a second contact component configured to contact the first expandable member near the second directional channel, the first chamber, the first contact component of the first movable component, and the second contact component of the second movable component substantially surround the first expandable member, the first movable component or a portion thereof is configured to slide within the first directional channel such that the first movable component extends out of or further away from the body of the oral drug dosage form along the axis, and the second movable component or a portion thereof is configured to slide within the second directional channel such that the second movable

component extends out of or further away from the body of the oral drug dosage form along the axis; one or more fluid inlets operably connected to the first chamber; a first stopper configured to engage the first movable component in an extended position; a second stopper configured to engage the second movable component in the extended position; a second chamber configured to comprise at least a portion of the second expandable member; a third directional channel operably connected to the second chamber, wherein the third directional channel comprises a curved channel, the third movable component comprises a contact component configured to contact the second expandable member near the third directional channel, the second chamber and the contact component of the third movable component substantially surround the second expandable member, the third movable component or a portion thereof is configured to rotate on the first shaft by the contact component sliding on the third directional channel such that the third movable component extends out of or further away from the body of the oral drug dosage form, and the one or more fluid inlets are operably connected to a third chamber; the third chamber configured to comprise at least a portion of the third expandable member; a fourth directional channel operably connected to the third chamber, wherein the fourth directional channel comprises a curved channel, the fourth movable component comprises a contact component configured to contact the third expandable member near the fourth directional channel, the third chamber and the contact component of the fourth movable component substantially surround the third expandable member, the fourth movable component or a portion thereof is configured to rotate on the second shaft by the contact component sliding on the fourth directional channel such that the fourth movable component extends out of or further away from the body of the oral drug dosage form, and the one or more fluid inlets are operably connected to the third chamber; and a drug. The oral drug dosage form is configured with a pre-administration status in a compact form and a post-administration status in an unfolded form that provides gastric retention, and the post-administration status in the unfolded form of the oral drug dosage form is at least partially due to the expansion of the first expandable member, the second expandable member, and the third expandable member in the presence of gastrointestinal fluid.

Provided is an oral drug dosage form for gastric retention. The oral drug dosage form comprises: an expandable member; a first movable component and a second movable component, wherein the first movable component and the second movable component

are configured such that at least a portion of each movable component can extend out of or further away from a body of the oral drug dosage form by a force provided by the expandable member, the first movable component and the second movable component are configured to rotate in opposite directions on a shared shaft, and the movable component comprises a tracking marker; the body comprising a chamber configured to comprise at least a portion of the expandable member; a first directional channel and a second directional channel operably connected to the chamber, wherein the first directional channel and the second directional channel are curved and configured around the shared shaft, the first movable component comprises a first contact component configured to contact the expandable member near the first directional channel, the first contact component is rudder-shaped and configured to travel in the first directional channel such that the first movable component rotates out of or farther away from the body of the oral drug dosage form relative to the shared shaft, the second movable component comprises a second contact component configured to contact the expandable member near the second directional channel, the second contact component is rudder-shaped and configured to travel in the second directional channel such that the second movable component rotates out of or farther away from the body of the oral drug dosage form relative to the shared shaft, and one or more fluid inlets are operably connected to the chamber; a stopper configured to engage the first movable component and the second movable component in an extended position; and a drug. The oral drug dosage form is configured with a pre-administration status in a compact form and a post-administration status in an unfolded form that provides gastric retention, and the post-administration status in the unfolded form of the oral drug dosage form is at least partially due to the expansion of the expandable member in the presence of gastrointestinal fluid.

Provided is an oral drug dosage form for gastric retention. The oral drug dosage form comprises: an expandable member, wherein the expandable member is at least partially wrapped with a semipermeable membrane; a first movable component and a second movable component, wherein the first movable component and the second movable component are configured such that each movable component is rotated around a separate shaft in a direction perpendicular to a positioning plane by a force provided by the expandable member, and the movable component comprises a tracking marker; and a body comprising a first connection point of the first movable component and a second

connection point of the second movable component, wherein each connection point is configured to provide a separate axis for rotation of the first movable component and the second movable component, each movable component comprises a contact component configured to contact the expandable member or the semipermeable material, a first stopper and a second stopper are configured to engage the first movable component and the second movable component in an extended position, respectively. The oral drug dosage form is configured with a pre-administration status in a compact form and a post-administration status in an unfolded form that provides gastric retention, and the post-administration status in the unfolded form of the oral drug dosage form is at least partially due to the expansion of the expandable member in the presence of gastrointestinal fluid.

In some embodiments, the number of the movable components is two or more. In some embodiments, the number of the movable components is selected from two, three, four, five, six, seven, eight, nine, and ten.

In some embodiments, the oral drug dosage form is configured with a pre-administration status in a compact form and a post-administration status in an unfolded form that provides gastric retention.

In some embodiments, the expandable member located within the chamber comprises a tracking marker. In some embodiments, the expandable member located within the chamber comprises an expandable material. In some embodiments, the expandable material is selected from one or more of a water-absorbing expandable material, an oil-absorbing expandable material, an oil- and water-absorbing expandable material, and an elastomer. In some embodiments, the expandable member located within the chamber comprises a swelling material. In some embodiments, the expandable material is admixed with a tracking marker material.

In other aspects, provided herein is an oral drug dosage form comprising: a body comprising an expandable member located within a chamber; a movable component comprising a tracking marker; a drug component located at the body and/or the movable component; and a shared shaft on which the movable component or a portion thereof is configured to rotate.

In some embodiments, the number of the movable components is two or more. In some embodiments, the number of the movable components is selected from two, three, four,

five, six, seven, eight, nine, and ten.

In some embodiments, the movable components or portions thereof are configured to rotate in opposite directions on the shared shaft.

In some embodiments, the oral drug dosage form is configured with a pre-administration status in a compact form and a post-administration status in an unfolded form that provides gastric retention.

In some embodiments, the expandable material is selected from one or more of a water-absorbing expandable material, an oil-absorbing expandable material, an oil- and water-absorbing expandable material, and an elastomer. In some embodiments, the expandable member located within the chamber comprises a swelling material. In some embodiments, the expandable material is admixed with a tracking marker material.

In some embodiments, the tracking marker is located within the chamber. In some embodiments, the expandable member located within the chamber comprises the tracking marker. In some embodiments, the expandable member located within the chamber comprises a swelling material. In some embodiments, the swelling material is admixed with a tracking marker material. In some embodiments, the swelling material is not admixed with the tracking marker material.

In some embodiments, the swelling material is selected from one or more of sodium alginate, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, polyethylene oxide, polyvinyl alcohol, microcrystalline cellulose, croscarmellose sodium, carboxymethylcellulose sodium, polyvinylpyrrolidone, sodium carboxymethyl starch, and polyethylene glycol. In some embodiments, the swelling material further comprises a salt or a mixture of salts. In some embodiments, the salt is selected from one or more of a sodium salt, a magnesium salt, a potassium salt, and an ammonium salt.

In some embodiments, the drug in the drug component of the oral drug dosage form described herein may be any drug. In some embodiments, the pharmaceutically active material is selected from one or more of a small molecule compound, a polypeptide, a protein, a nucleic acid, an antibody, a cell-containing hydrogel, and a microorganism. In some embodiments, the pharmaceutically active material is selected from one or more of a small molecule compound, a polypeptide, and a protein.

In some embodiments, the small molecule compound is selected from tofacitinib,

lidocaine, 11-di-deuterated ethyl linoleate, 16-dehydropregnenolone, 3,5-diiodothyronine, 5-fluoro-2-deoxycytidine, 6-mercaptopurine, abacavir, abiraterone, acamprosate, acarbose, aceclidine, aceclofenac, acetylneuraminic acid, acetaminophen, acetylcysteine, acetyl-L-carnitine, acetylsalicylic acid, acyclovir, acipimox, acitazanolast, acridinium bromide, acolbifene, acotiamide, acrivastine, actarit, adapalene, adefovir dipivoxil, afatinib, agomelatine, aildenafil, alarelin acetate, alatrofloxacin, albendazole, albuterol sulfate, alcaftadine, alendronic acid, alfacalcidol, alfaxalone, alfentanil, alfuzosin, aliskiren, alitretinoin, allisartan isoproxil, allopregnanolone, allopurinol, almotriptan, alogliptin, alosetron, alphaketoglutaric acid, alpha-lipoic acid, alprazolam, alprostadil, altretamine, aluminum sulfate, alvimopan, amantadine, ambrisentan, ambroxol, amphetamine, amphetamine sulfonated divinylbenzene, amifampridine, amifostine, amikacin, amiloride, aminoacetyl, levulinic acid, aminopterin, amiodarone, amisulpride, amitriptyline, amlexanox, amlodipine, ammonium lactate, amodiaquine, amorolfine, amosulalol, amoxicillin, ampicillin, ampiroxicam, amrinone, amrubicin, amtolmetin guacil, anagliptin, anagrelide, anamorelin, anastrozole, ancrod, andrographolide, anecortave, anidulafungin, aniracetam, anistreplase, anlotinib, antazoline, antroquinonol, apatinib, apixaban, apomorphine, apremilast, Aprepitant, apricitabine, aranidipine, arbekacin, arformoterol, argatroban, aripiprazole, armodafinil, arsenious acid, artemether, artenimol, artesunate, asenapine, asimadolin, astragaloside, asunaprevir, atazanavir, atenolol, atomoxetine, atorvastatin, atovaquone, atrasentan, atropine, auranofin, avanafil, avibactam, axitinib, azacitidine, cytidine, azasetron, azelaic acid, azelastine, azelnidipine, azilsartan, azimilide, aztreonam, azvudine, baclofen, bafetinib, baicalin, balofloxacin, balsalazide, bambuterol, baricitinib, barnidipine, bazedoxifene, beclomethasone dipropionate, bedoradrine, belotecan, benazepril, bencycloquidium bromide, bendamustine, benidipine, benserazide, benzalkonium chloride, benznidazole, benzocaine, benzoyl peroxide, benzydamine, bepotastine, beractant, beraprost, besifloxacin, besifovir, besipirdine, β -elemene, betahistine, betaine, betamethasone, betamipron, betaxolol, bethanechol, uracholine, betrixaban, bevacizumab, bexarotene, bezafibrate, biapenem, bicalutamide, bicyclol, bifico, bilastine, bimatoprost, bismuth subgallate, ecabet, bisoprolol, bitespiramycin, bleomycin, blonanserin, boceprevir, bortezomib, bosentan, bosutinib, bovactant, brexpiprazole, brimonidine, brinzolamide, brivaracetam, brivudine, bromazepam,

bromfenac, bromocriptine, brotizolam, bucindolol, bucladesine, budesonide, budipine, buflomedil, bunazosin, bupivacaine, buprenorphine, bupropion, burixafor, buserelin, buspirone, busulfan, butenafine, butorphanol, butylphthalide, cabazitaxel, cabergoline, cabozantinib, cadoxifloxacin, caffeine, calcipotriol, calcitriol, calfactant, calmangafodipir, camostat, camptothecin, canagliflozin, candesartan, cangrelor, capecitabine, captopril, carbamazepine, carbetocin, carbidopa, carbinoxamine, carbocysteine, carboplatin, carfilzomib, carginic acid, cariprazine, carmustine, carteolol, carumonam, carvedilol, caspofungin, catechin, cediranib, cefaclor, cefdroxil, cefathiamidine, cefcapene, cefdinir, cefditoren pivoxil, cefepime, cefetamet pivoxil, cefminox, cefoperazone, cefoselis, cefotaxime, cefotiam, ceftazidime, cefpirome, cefpodoxime, cefprozil, ceftaroline fosamil, ceftazidime, ceftibuten, ceftobiprole medocartil, ceftriaxone, cefuroxime, celecoxib, celgosivir, celiprolol, ceritinib, cetilistat, cetirizine, cetraxate, cevimeline, chenodeoxycholic acid, chlormadinone acetate, chlorogenic acid, chlorpheniramine, chlorthalidone, cholecalciferol, cholic acid, choline glycerophosphate, choline fenofibrate, ciclesonide, ciclopirox olamine, ciclosporin, cidofovir, cidozepin, cilastatin, cilazapril, cilnidipine, cilostazol, cimetidine, cinacalcet, cinepazide, cinitapride, ciprofibrate, ciprofloxacin, cisatracurium besylate, cisplatin, citalopram, citicoline, citrulline, cladribine, clarithromycin, clavulanic acid, clazosentan, clevidipine, clevudine, clioquinol, clobazam, clobetasol, clofibrate, clofazimine, clomipramine, clonazepam, clonidine, clopidogrel, clotrimazole, clozapine, cobamamide, cobicistat, codeine, colchicine, cholecalciferol, colesevelam, colestilan, colfosceril palmitate, conivaptan, 11-cortexolone 17 α -vinyl propionate, cridanimod, crizotinib, cromoglicic acid, cyanocobalamin, cyclizine lactate, cyclobenzaprine, cyclophosphamide, cyclosporin, cyproterone, cytarabine, dabigatran etexilate, dabrafenib, daclatasvir, dacomitinib, dalbavancin, dalcetrapib, aminopyridine, dalfopristin, danazol, dantrolene, danusertib, dapiprazole, dapivirine, dapoxetine, dapsone, darifenacin, darunavir, dasabuvir, dasatinib, daunorubicin, decitabine, deferasirox, deflazacort, delafloracin, delamanid, delapril, delavirdine, denibulin, deoxyandrographolide, desflurane, desipramine, loratadine, desmopressin, desogestrel, desonide, desvenlafaxine, dextromethorphan, verteporfin, levodopa, venlafaxine, dexamethasone, dexamethasone cipeclate, dextroamphetamine, dexanabinol, iron-dextran, dexketoprofen tromethamine, dextansoprazole, dexmedetomidine, methylphenidate, dexrazoxane, sotalol, d-sucrose,

dextromethorphan, dextropropoxyphene, diacerein, diacetylmorphine, dianhydrogalactitol, diazepam, diazoxide choline, diclofenac, dichlorphenamide, dicycloplatin, didanosine, dienogest, difluprednate, digoxin, linolenic acid, dihydroergocristine, dihydroergotamine, diltiazem, dimesna, dimethyl fumarate, dimiracetam, dinoprostone, diphenylcyclopropenone, dipyridamole, tobramycin, disufenton, disulfiram, dithranol, methadone, docarpamine, docetaxel, glycol, dofetilide, dolasetron, dolutegravir, domperidone, sorafenib, donepezil, dopamine, doripenem, dorzolamide, dosmalfate, doxacurium chloride, doxazosin, doxepin hydrochloride, doxercalciferol, doxifluridine, doxofylline, doxorubicin, doxycycline, doxylamine succinate, dronabinol, dronedarone, drospirenone, droxidopa, D-tagatose, duloxetine, dutasteride, ebastine, eberconazole, ebselen, ecabet, isoconazole, ecopipam, edaravone, edoxaban, efavirenz, efinaconazole, eflornithine, efonidipine, egualen, eicosapentaenoic acid monoglyceride, elagolix, eldecalcitol, elesclomol, eletriptan, eltrombopag, elvitegravir, emedastine, empagliflozin, emricasan, emtricitabine, enalapril, enclomiphene, tamoxifen, enoxacin, enprostil, entacapone, entecavir, entinostat, enzalutamide, epalrestat, eperisone, ephedrine, epinastine, epinephrine, epirubicin, epitinib, eplerenone, epoprostenol, epristeride, eprodisate, eprosartan, eptaplatin, erdosteine, eribulin, erlotinib, ertapenem, erythromycin, escitalopram, esketamine, ketamine, eslicarbazepine, esmolol, esomeprazole, estetrol, estradiol, estratest, eszopiclone, ethambutol, ethaselen, ethinylestradiol, ethyl fumarate, ethinyl estradiol, etidronic acid, etimicin, etizolam, etodolac, etonogestrel, etoposide, etoricoxib, etravirine, eupatilin, everolimus, exemestane, ezetimibe, fadrozole, falecalcitriol, famciclovir, famotidine, fampridine, faropenem, fasoracetam, fasudil, favipiravir, febarbamate, febuxostat, tromethamine, felodipine, fenfluramine, fenofibrate, fenoldopam, fenoterol, fenretinide, fentanyl, fenticonazole, ferric citrate, ferric maltol, fesoterodine, fexinidazole, fexofenadine, fidaxomicin, fimasartan, finafloxacin, finasteride, fingolimod, flecainide, fleroxacin, flibanserine, flomoxef, floxuridine, fluconazole, fludarabine, flumazenil, flunisolide, fluocinolone, fluorouracil, fluoxetine, flupirtine, flurbiprofen, flurithromycin, fluticasone, flutrimazole, fluvastatin, fluvoxamine, folic acid, folinic acid, fomepizole, formestane, formoterol, forodesine, fosamprenavir, fosaprepitant, fosfomycin, fosinopril, fosmidomycin, fosphenytoin, fospropofol, fotemustine, frovatriptan, fruquintinib, furosteine, fulvestrant, furosemide, fusidic acid, gabapentin, gabapentin enacarbil,

gabexate, gadobutrol, gadoversetamide, galantamine, gallium nitrate, gambogic acid, ganaxolone, ganirelix, gareoxacin, gatifloxacin, gefitinib, gemcitabine, gemfibrozil, gemifloxacin, gentamicin, gentiopicroside, gepirone, gestodene, gestrinone, timolol, glatiramer, glibenclamide, gliclazide, glimepiride, glipizide, glufosfamide, glutamine, glycerol benzene, glycopyrronium, glycopyrronium bromide, glycyrrhizic acid, golotimod, gosogliptin, granisetron, guaifenesin, guaimesal, guanfacine, gusperimus, halobetasol, halofantrine, halometasone, hyaluronic acid, hydrochlorothiazide, hydrocodone, hydrocortisone, hydromorphone, hydroxocobalamin, hydroxyurea, hydroxychloroquine, hydroxyprogesterone caproate, hypericin, ibodutant, ibrutinib, ibudilast, ibuprofen, ibutilide, epimedium, iclaprim, icosapent, icosapent ethyl, icotinib, idebenone, iodoxuridine, ifetroban, iguratimod, ilaprazole, iloperidone, iloprost, imatinib, imidafenacin, imidapril, imipenem, imiquimod, imrecoxib, incadronic acid, indacaterol, indapamide, indeloxazine, indinavir, indisetron, indomethacin, indoramine, inecalcitol, ipragliflozin, ipratropium, ipratropium bromide, iptakalim, irbesartan, irinotecan, irinotecan sucrosofate, irofulven, irsogladine, isoflurane, isoniazid, isopropyl unoprostone, isosorbide, isosteviol, isotretinoin, isradipine, istradefylline, itopride, itraconazole, ivabradine, ixabepilone, ketamine, ketoconazole, ketoprofen, ketorolac, ketotifen, kukoamine, lacidipine, lacosamide, lactitol, laflunimus, lafutidine, lamivudine, lamotrigine, landiolol, laninamivir, lanoconazole, lansoprazole, lanthanum carbonate, lapatinib, laquinimod, lasofoxifene, latanoprost, ledipasvir, leflunomide, lenalidomide, lentinan, lercanidipine, letepirim, letrozole, leucine, leuprorelin, levalbuterol, levamisole, levamlodipine, levetiracetam, levobupivacaine, levocabastine, levocarnitine, levocetirizine, levodopa, levofloxacin, levonorgestrel, levonorgestrel butanoate, levophencynonate hydrochloride, levornidazole, L-glutamine, lidocaine, ligustrazine hydrochloride, limaprost, linagliptin, linezolid, liothyronine, liranafate, lisinopril, lodenafil, lofexidine, lomefloxacin, lomerizine, lonidamine, lopinavir, loratadine, lorazepam, lornoxicam, losartan, losartan potassium, loteprednol, lovastatin, loxoprofen, levapraziquantel, lumiracoxib, mafenide, magnesium isoglycyrrhizinate, mangafodipir, manidipine, mannitol, maraviroc, maribavir, masitinib, mebendazole, nitrogen mustard, mecobalamin, megestrol, meloxicam, memantine, menatetrenone, mepacrine, quinacrine, mequinol, mercaptamine, mercaptopurine, meropenem, mesalazine, metacavir, metadoxine, metamizole sodium, metaxalone, metergoline, metformin,

methadone, methazolamide, methotrexate, methoxyflurane, methylvaleric acid, methylnaltrexone, methylphenidate, 6-methylprednisolone, methylprednisolone aceponate, methylene blue, metyrosine, metoclopramide, metoprolol, metronidazole, metyrapone, mibefradil, miconazole, midazolam, midodrine, midostaurin, mifepristone, miglitol, milnacipran, milrinone, miltefosine, minaprine, minocycline, minodronic acid, minoxidil, mirabegron, mirodenafil, mirtazapine, misoprostol, mitiglinide, mitoxantrone, mivotilate, mizolastine, mizoribine, moclobemide, modafinil, doxycycline, modipafant, moexipril, mofezolac, morpholone, mometasone furoate, glycyrrhizic acid, monobenzene, luminol, monoterpene perillyl alcohol, montelukast, moricizine, tigecycline, morinidazole, morphine, morphine glucuronide, mosapride, moxidectin, moxifloxacin, moxonidine, mozavaptan, mupirocin, mycophenolate mofetil, myristyl nicotinate, nabumetone, N-acetylcysteine, nadifloxacin, nadolol, naftifine, naftopidil, nalbuphine, nalfurafine, nalmefene, naloxegol, naloxone, naltrexone, nandrolone decanoate, naphazoline, naphthoquine, naproxen, naratriptan, nasaruplase, nateglinide, nebivolol, nedaplatin, nedocromil, nelarabine, nelfinavir, nemonapride, nemonoxacin, neostigmine, nepadutant, nepafenac, nepicastat, neratinib, neridronic acid, netilmicin, netupitant, nevirapine, niacin, nicardipine, nicergoline, nicorandil, nicotiflorin, nicotine, nicousamide, nifedipine, nifekalant, nifeviroc, nifurtimox, nifurzide, nikkomycin, nilotinib, nilutamide, nilvadipine, nimesulide, nimodipine, morinidazole, nisoldipine, nitazoxanide, nitisinone, nitrendipine, nitroglycerin, nizatidine, nolatrexed, nomegestrol, norelgestromin, norepinephrine, norethisterone, norfloxacin, norgestimate, obeticholic acid, octenidine, octahydroacridine succinate, ofloxacin, olanzapine, olaparib, olesoxime, olmesartan, indacaterol, olodaterol, olopatadine, olprinone, olsalazine, oltipraz, omarigliptin, omeprazole, omoconazole, onapristone, ondansetron, opipramol, methylphenidate, orcinoside, oritavancin, orlistat, ornithine phenylacetate, ornoprostil, oseltamivir, ospemifene, oteracil potassium, oxaliplatin, oxaloacetic acid, oxazepam, oxcarbazepine, oxfendazole, oxiracetam, oxybutynin, oxycodone, oxymetazoline, oxymorphone, oxytocin, ozagrel, ozenoxacin, paclitaxel, paliperidone, pamidol, palonosetron, palovarotene, panipenem, panobinostat, pantoprazole, paracetamol, parecoxib, paricalcitol, paritaprevir, parogrelil, paromomycin, paroxetine, patupilone, pazopanib, pazufloxacin, pelubiprofen, pemetrexed, pemirolast, pemirolast potassium, penciclovir, penicillidide

hydrochloride, pentamidine, pentetic acid, pentostatin, pentoxifylline, peramivir, perampanel, thioacetazone, perfluoropentane, perfluorooctyl bromide, pergolide, perifosine, perindopril, perospirone, phenchlobenpyrrone, phenoxybenzamine hydrochloride, phentermine, topiramate, phentermine, phentolamine, phenytoin, picibanil, pidotimod, pilsicainide, pimavanserin, pimecrolimus, pimobendan, pioglitazone, piperidone, pipecurium bromide, piperacillin, piperazine, piracetam, pirarubicin, pirfenidone, pirmenol, pirotinib, piroxicam, pitavastatin, pixantrone, pleconaril, plerixafor, podofilox, pomalidomide, ponatinib, porfimer, posaconazole, clavulanic acid, pradefovir, aminopterin, pramipexole, pramiracetam, pranlukast, prasterone, prasugrel, pravastatin, prazosin, prednimustine, prednisolone, prednisone, pregabalin, prempo, prilocaine, procaterol, prochlorperazine, progestogen dienogest, proguanil, promethazine, propafenone, propagermanium, propofol, propranolol, proxodolol, prucalopride, prulifloxacin, prussian blue, pseudoephedrine, puerarin, puquitinib, pyrazinamide, pyridoxamine, pyridoxine, pyrimethamine, pyronaridine, malaridine, quazepam, quetiapine, quinapril, quinidine, quinine, quizartinib, rabeprazole, racecadotril, radotinib, raloxifene, raltegravir, raltitrexed, ramatroban, rozerem, ramipril, ramosetron, ranitidine, ranolazine, rasagiline, rebamipide, reboxetine, ibuprofen, naproxen, glycopyrronium bromide, diclofenac, mebendazole, progesterone, zoledronic acid, regorafenib, remifentanyl, repaglinide, repirinast, amlexanox, chlorcyclizine, bucillamine, guanabenz, mazindol, naltrexone, nitisinone, retigabine, rosiglitazone, resiquimod, retagliptin, retapamulin, retigabine, retinoic acid, revaprazan, rhein, ribavirin, rifabutin, rifampicin, rifamycin, rifapentine, rifaximin, rilapladib, rilpivirine, rilpivirine hydrochloride, riluzole, rimexolone, riociguat, risedronic acid, risperidone, ritonavir, rivaroxaban, rivastigmine, rizatriptan, roflumilast, rokitamycin, rolapitant, ropinirole, ropivacaine, rosiglitazone, rosuvastatin, rotigotine, roxithromycin, rubitecan, rufinamide, rufloxacin, rupatadine, ruxolitinib, levornidazole, sacubitril, safinamide, salbutamol, salicylic acid, salmeterol, salvicine, 3-formylamino-4-hydroxynaltrexone, amlodipine, sapropterin, saquinavir, saracatinib, sarpogrelate, saxagliptin, scopolamine, secnidazole, selegiline, selumetinib, seratrovast, seratrovast, celiprolol, sertaconazole, sertaconazole nitrate, sertraline, sesquiterpene, sevelamer, sevoflurane, sibutramine, sildenafil, silodosin, simeprevir, simotinib, simvastatin, sinotecan, siponimod, sirolimus, sitafloxacin, sitagliptin, sivelestat, sizofran, sizofiran, sizofiran, modafinil, sobuzosine, aescin, benzoic acid,

cromolyn, glycididazole, gualenic acid, hyaluronic acid, ibandronic acid, hydroxybutyric acid, phenylacetic acid, phenylbutyric acid, pyruvic acid, sofosbuvir, solifenacin, sorafenib, sorbitol, sparfloxacin, spirapril, stavudine, stepronin, stiripentol, strontium ranelate, suftalan zine, sugammadex, sulbactam, sulcardine, methoxypyrazine, sulfasalazine, surufatinib, sumatriptan, sunitinib, suplatast tosilate, suramin sodium, verapamil, rilpivirine, tacalcitol, tachocomb, tacrine, tacrolimus, tadalafil, tafamidis, tafenoquine, talaporfin, talipexole, tatirelin, tamibarotene, tamoxifen, tamsulosin, tapentadol, tarafenacin, tasimelteon, tasquinimod, tazarotene, tazobactam, tebipenem pivoxil, tecovirimat, tedisamil, tedizolid, tegafur, tegaserod, teicoplanin, telaprevir, telatinib, telbivudine, telithromycin, telmisartan, temocapril, temoporfin, temozolomide, sirolimus, teneligliptin, tenofovir, tenoxicam, teprenone, terazosin, terbinafine, terguride, teriflunomide, tesofensine, tetracycline, tetrathiomolybdate, tetrahydrozoline, tyzine, thalidomide, thienorphine, thiotepa, ticagrelor, ticlopidine, tigecycline, tiludronic acid, timolol, timolol maleate, tinidazole, methylnitroimidazole, tioconazole, tiopronin, tiotropium bromide, tipepidine, tipifarnib, tipranavir, tirapazamine, tiritazad, tirofiban, oxcarbazepine, tirofiban, tizanidine, tobramycin, tocopherolsol, tofacitinib, tofogliflozin, tolcapone, tolimidone, toloperisone, tolterodine, tolvaptan, tonabersat, topiramate, topiroxostat, topotecan, torasemide, toremifene, tosedostat, tosufloxacin, trabectedin, tramadol, trametinib, trandolapril, tranexamic acid, tranilast, trantinterol, trazodone, trelagliptin, treosulfan, tretinoin, triamcinolone acetonide, triazolam, trichlormethiazide, triciribine, triclazendazole, triclocarban, trientine, trilostane, trimebutine, trimegestone, trimethoprim, tropisetron, trospium chloride, trovafloxacin, troxipide, tulobuterol, tylerdipine, ubenimex, ubidecarenone, udenafil, ulinastatin, ulipristal, ulobetasol, urapidil, valacyclovir, valdecoxib, valganciclovir, valrubicin, valsartan, vandetanib, vanoxerine, vardenafil, varenicline, velusetrag, vemurafenib, venlafaxine, verapamil, veregen, vernakalant, verteporfin, vesnarinone, vesnaretinone, vicagrel, vigabatrin, vilanterol, vilazodone, vildagliptin, voriconazole, vorinostat, vortioxetine, xemilofiban, milofiban, emitasvir, yonkenafil, zafirlukast, zalcitabine, zaleplon, zaltoprofen, zanamivir, zidovudine, ziprasidone, zofenopril, zoledronic acid, zolmitriptan, zolpidem, zonisamide, zopiclone, zotepine, zucapsaicin, zuclopenthixol, tolvaptan and a pharmaceutically acceptable salt, an ester, a prodrug, a hydrate, a deuterated compound, and a stereoisomer thereof.

In some embodiments, the polypeptide is selected from one or more of insulin, antidiuretic hormone, calcitonin, calcitonin gene-related peptide, parathyroid hormone, luteinizing hormone, erythropoietin, tissue plasminogen activator, growth hormone, adrenocorticotrophic hormone, interleukin, enkephalin, epinephrine, GLP-1 receptor agonist, semaglutide, liraglutide, dulaglutide, exenatide, octreotide, teriparatide, vancomycin, linaclotide, plecanatide, voclosporin, tatrelin, acetylamino pitressin, macimorelin, and glucagon-like peptide-2 (GLP-2) analogs (e.g., teduglutid).

In some embodiments, the protein is selected from proteins related to medicine, agriculture, scientific research, and other industrial fields. In some embodiments, the protein is selected from one or more of a blood factor, a colony stimulating factor, an interleukin, a growth factor, a tumor necrosis factor (TNF), and an enzyme. In some embodiments, the protein is selected from asparaginase, glutaminase, arginase, arginine deaminase, adenosine deaminase, ribonuclease, cytosine deaminase, trypsin, chymotrypsin, papain, epidermal growth factor (EGF), insulin-like growth factor (IGF), transforming growth factor (TGF), nerve growth factor (NGF), platelet-derived growth factor (PDGF), bone morphogenetic protein (BMP), fibroblast growth factor, somatostatin, somatostatin, a colony stimulating factor (CSF), a blood coagulation factor, a tumor necrosis factor, interferon, gastrointestinal peptide, vasoactive intestinal peptide (VIP), cholecystokinin (CCK), gastrin, secretin, hormone, pancreatic enzyme, superoxide dismutase, thyrotropin-releasing hormone (TRH), thyroid stimulating hormone, leuteinizing hormone, luteinizing hormone releasing hormone (LHRH), tissue plasminogen activator, receptor antagonist (IL-1RA), leptin, auxin, granulocyte-macrophage colony-stimulating factor (GM-CSF), adenosine deaminase, uricase, asparaginase, asparaginase, chorionic gonadotropin, heparin, atrial natriuretic peptide, hemoglobin, a retroviral vector, relaxin, cyclosporine, oxytocin, ankyrin repeat protein, and an affibody.

In some embodiments, the nucleic acid refers to an oligomer or polymer comprising at least two linked nucleotides or nucleotide derivatives, including deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) that are linked together by phosphodiester bonds or other phosphates. In some embodiments, the nucleic acid includes a DNA molecule and a RNA molecule. In some embodiments, the nucleic acid may be single-stranded or double-stranded, and may be a cDNA.

In some embodiments, the antibody is selected from Abagovomab, Abciximab,

Actoxumab, Adalimumab, Adecatumumab, Aducanumab, Afelimomab, Afutuzumab, Alacizumab pegol, ALD518, Alemtuzumab, Alirocumab, Altumomabpentetate, Amatuximab, Anatumomabmafenatox, Anifrolumab, Anrukinzumab, Apolizumab, Arcitumomab, Aselizumab, Atinumab, Atlizumab, Atorolimumab, Bapineuzumab, Basiliximab, Bavixumab, Bectumomab, Belimumab, Benralizumab, Bertilimumab, Besilesomab, Bevacizumab, Bezlotoxumab, Biciromab, Bimagrumab, Bivatuzumab mertansine, Blinatumomab, Blosozumab, Brentuximabvedotin, Briakinumab, Brodalumab, Canakinumab, Cantuzumab mertansine, Cantuzumabravtansine, Caplacizumab, Capromabpendetide, Carlumab, Catumaxomab, cBR96-doxorubicinimmuno conjugate, Cedelizumab, Certolizumabpegol, Cetuximab, Citatuzumabbogatox, Cixutumumab, Clazakizumab, Clenoliximab, Clivatuzumabtraxetan, Conatumumab, Concizumab, Crenezumab, Dacetuzumab, Daclizumab, Dalotuzumab, Daratumumab, Demcizumab, Denosumab, Detumomab, Dorlimomabaritox, Drozitumab, Duligotumab, Dupilumab, Dusigitumab, Ecomeximab, Eculizumab, Edobacomab, Edrecolomab, Efalizumab, Efungumab, Eldelumab, Elotuzumab, Elsilimomab, Enavatuzumab, Enlimomab pegol, Enokizumab, Enoticumab, Ensituximab, Eritumomabcituxetan, Epratuzumab, Erlizumab, Ertumaxomab, Etaracizumab, Etrolizumab, Evolocumab, Exbivirumab, Fanolesomab, Faralimumab, Farletuzumab, Fasinumab, FBT005, Felvizumab, Fezakinumab, Ficlitzumab, Figitumumab, Flanvotumab, Fontolizumab, Foralumab, Foravirumab, Fresolimumab, Fulranumab, Futuximab, Galiximab, Ganitumab, Gantenerumab, Gavilimumab, Gemtuzumabozogamicin, Gemtuzumab, Gevokizumab, Girentuximab, Glembatumumabvedotin, Golimumab, Gomiliximab, Guselkumab, Ibalizumab, Ibiritumomab tiuxetan, Icrucumab, Igovomab, IMAB362, Imciromab, Imgatuzumab, Inclacumab, Indatuximabravtansine, Infliximab, Inolimomab, Inotuzumab ozogamicin, Intetumumab, Ipilimumab, Iratumumab, Itolizumab, Ixekizumab, Keliximab, Labetuzumab, Lambrolizumab, Lampalizumab, Lebrikizumab, Lemalesomab, Lerdelimumab, Lexatumumab, Libivirumab, Ligelizumab, Lintuzumab, Lirilumab, Lodelcizumab, Lorvotuzumabmertansine, Lucatumumab, Lumiliximab, Mapatumumab, Margetuximab, Maslimomab, Matuzumab, Mavrilimumab, Mepolizumab, Metelimumab, Milatuzumab, Minretumomab, Mitumomab, Mogamulizumab, Morolimumab, Motavizumab, motavizumab, Moxetumomabpasudotox, Muromonab-CD3, Nacolumabtafenatox,

Namilumab, Naptumomabestafenatox, Narnatumab, Natalizumab, Nebacumab, Necitumumab, Nerelimomab, Nesvacumab, Nimotuzumab, Nivolumab, Nofetumomabmerpentan, Ocaratuzumab, Ocrelizumab, Odulimomab, Ofatumumab, Olaratumab, Olokizumab, Omalizumab, Onartuzumab, Ontuxizumab, Oportuzumabmonatox, Oregovomab, Orticumab, Otelixizumab, Otlertuzumab, Oxelumab, Ozanezumab, Ozoralizumab, Pagibaximab, Palivizumab, Panitumumab, Pankomab, Panobacumab, Parsatuzumab, Pascolizumab, Pateclizumab, Patritumab, pembrolizumab, Pemtumomab, Perakizumab, Pertuzumab, Pexelizumab, Pidilizumab, Pinatuzumabvedotin, Pintumomab, Placulumab, Polatuzumabvedotin, Ponezumab, Priliximab, Pritoxaximab, Pritumumab, PRO140, Quilizumab, Racotumomab, Radretumab, Rafivirumab, Ramucirumab, Ranibizumab, Raxibacumab, Regavirumab, Reslizumab, Rilotumumab, Rituximab, Robatumumab, Roledumab, Romosozumab, Rontalizumab, Rovelizumab, Ruplizumab, Samalizumab, Sarilumab, Satumomabpendetide, Secukinumab, Seribantumab, Setoxaximab, Sevirumab, SGN-CD19A, SGN-CD33A, Sibrotuzumab, Sifalimumab, Siltuximab, Simtuzumab, Siplizumab, Sirukumab, Solanezumab, Solitomab, Sonepcizumab, Sontuzumab, Stamulumab, Sulesomab, Suvizumab, Tabalumab, Tacatuzumabtetraxetan, Tadocizumab, Talizumab, Tanezumab, Taplitumomabpaptox, Tefibazumab, Telimomabaritox, Tenatumomab, Teneliximab, Teplizumab, Teprotumumab, TGN1412, Ticilimumab, tremelimumab, Tigatuzumab, TNX-650, atlizumab, Toralizumab, Tositumomab, Tovetumab, Tralokinumab, Trastuzumab, TRBS07, Tregalizumab, Tremelimumab, Tucotuzumabcelmoleukin, Tuvirumab, Ublituximab, Urelumab, Urtoxazumab, Ustekinumab, Vantictumab, Vapaliximab, Vatelizumab, Vedolizumab, Veltuzumab, Vepalimomab, Vesencumab, Visilizumab, Volociximab, Vorsetuzumabmafodotin, Votumumab, Zalutumumab, Zanolimumab, Zatuximab, Ziralimumab, Zolimomab aritox, and a fragment thereof.

In some embodiments, the microorganism is selected from one or more of bacteria, viruses, fungi, actinomycetes, rickettsia, mycoplasma, chlamydia, and spirochete. In some embodiments, the microorganism is selected from probiotics. In some embodiments, the probiotic is selected from one or more of yeast, probiotic *Bacillus*, *Clostridium butyricum*, *Lactobacillus*, *Bifidobacterium*, and *Actinomyces*.

In some embodiments, the oral drug dosage form comprises an additional component, such as an outer coating. In some embodiments, the outer coating is a flavor coating. In

some embodiments, the outer coating is a sugar coating. In some embodiments, the outer coating is a decorative coating. In some embodiments, the outer coating is a color coating. In some embodiments, the outer coating is a film coating. In some embodiments, the outer coating is a polymeric coating. In some embodiments, the additional component is a label, such as: company name, abbreviation, or logo; a drug label or drug name (such as a drug brand name and/or a drug chemical name or abbreviation); the amount or strength of the drug; an identification barcode; or any combination thereof. In some embodiments, the additional component is a capsule shell.

Examples of oral drug dosage forms

For the purpose of illustrating and explaining the subject matter provided herein, certain oral drug dosage forms are described below.

Provided herein, in some aspects, is an oral drug dosage form configured to release a drug at a desired gastrointestinal location, the oral drug dosage form comprising: a drug component comprising a first erodible material admixed with a drug and a first tracking stripe embedded in the drug component; a non-erodible component not admixed with the drug, comprising a first tracking loop and a second tracking loop embedded in the non-erodible component, wherein the non-erodible component is associated with at least a portion of the drug component; and a delay component not admixed with the drug, the delay component comprising: a pH-based enteric member configured to erode at or above a pre-determined pH value; and an erodible delay member comprising a second erodible material, wherein the pH-based enteric member and the non-erodible component prevent erosion of the erodible delay member, and wherein the erodible delay member and the non-erodible component prevent erosion of the drug component, and wherein one surface of the first tracking loop is in direct contact with the erodible delay member. In some embodiments, the oral drug dosage form is configured to release a drug at, near, or downstream of the ileum of an individual, such as at any one or more of the cecum, ascending colon, transverse colon, descending colon, and/ or sigmoid colon.

Provided herein, in some aspects, is an oral drug dosage form configured to release a

drug at a desired gastrointestinal location, the oral drug dosage form comprising: two drug components comprising a first erodible material and a first visible material admixed with a drug; a non-erodible component not admixed with the drug, comprising a first tracking stripe embedded in the non-erodible component and located between the drug components, wherein the non-erodible component is associated with at least a portion of the drug component; and a delay component not admixed with the drug, the delay component comprising: a pH-based enteric member configured to erode at or above a pre-determined pH value; and an erodible delay member comprising a second erodible material, wherein the pH-based enteric member and the non-erodible component prevent erosion of the erodible delay member, and wherein the erodible delay member and the non-erodible component prevent erosion of the drug component. In some embodiments, the oral drug dosage form is configured to release a drug at, near, or downstream of the ileum of an individual, such as at any one or more of the cecum, ascending colon, transverse colon, descending colon, and/ or sigmoid colon. Provided herein, in some aspects, is an oral drug dosage form configured to release a drug at a desired gastrointestinal location, the oral drug dosage form comprising: a drug component comprising a first erodible material admixed with a drug and a first tracking stripe and a first tracking loop embeded in the drug component; a non-erodible component not admixed with the drug, comprising a second tracking loop embedded in the non-erodible component, wherein the non-erodible component is associated with at least a portion of the drug component; and a delay component not admixed with the drug, the delay component comprising: a pH-based enteric member configured to erode at or above a pre-determined pH value; and an erodible delay member comprising a second erodible material, wherein the pH-based enteric member and the non-erodible component prevent erosion of the erodible delay member, and wherein the erodible delay member and the non-erodible component prevent erosion of the drug component, and wherein one surface of the first tracking loop is in direct contact with the erodible delay member. In some embodiments, the oral drug dosage form is configured to release a drug at, near, or downstream of the ileum of an individual, such as at any one or more of the cecum, ascending colon, transverse colon, descending colon, and/ or sigmoid colon.

FIG. 1 provides a schematic diagram of an oral drug dosage form 100. The oral drug dosage form 100 comprises the non-erodible component 102 and the drug component

104. The non-erodible component comprises a barrier material that is impermeable to bodily fluids, and the drug component comprises a first erodible material admixed with a drug. The drug component 104 forms a layer comprising the top surface 106, the bottom surface 108, and one or more sides (e.g., 110), wherein the one or more sides of the layer of the drug component are bonded to, such as in direct contact with, the non-erodible component. The use of directional terms, such as top, bottom, and side, is intended to facilitate the description of the disclosure provided herein and should not be construed to limit the scope of the invention provided herein. The delay component of the oral drug dosage form 100 is not admixed with the drug and comprises: a pH-based enteric member configured to erode at or above a predetermined pH value; and an erodible delay member comprising a second erodible material. The pH-based enteric member and the non-erodible component prevent the erosion of the erodible delay member, and the erodible delay member and the non-erodible component prevent the erosion of the drug component. Specifically, in the oral drug dosage form 100 of FIG. 1, the delay component comprises a pair of layer sets of the first layer 112 of the erodible delay member, the first layer 118 of the pH-based enteric member, the second layer 122 of the erodible delay member, and the second layer 124 of the pH-based enteric member. The oral drug dosage form 100 is configured such that the top surface 106 of the layer of the drug component 104 is in direct contact with the bottom surface 114 of the first layer 112 of the erodible delay member, and the top surface 116 of the first layer 112 of the erodible delay member is in direct contact with the bottom surface 120 of the first layer 118 of the pH-based enteric member. The second layer set of the delay component is similarly arranged. Specifically, the bottom surface 108 of the layer of the drug component 104 is in direct contact with the second layer 122 of the erodible delay member, and the second layer 122 of the erodible delay member is in direct contact with the second layer 124 of the pH-based enteric member. As shown in FIG. 1A, the pH-based enteric members 118 and 124 and the non-erodible component 102 completely surround the erodible delay members 112 and 122 and the drug component 104.

The oral drug dosage form 100 of **FIG. 1** is configured such that upon administration to a human individual, the oral drug dosage form will begin the process of passing through the gastrointestinal system of the human individual, and once the oral drug dosage form 100 is affected by the gastrointestinal fluid having a suitable pH (such as

a pH of 5.5 or higher), the top surface 122 of the first layer 118 of the pH-based enteric layer and the bottom surface 126 of the second layer 124 of the pH-based enteric layer erode away from the oral drug dosage form 100 in the direction of arrows 128 and 130, respectively. At some time after administration to a human individual, the first and second layers of the pH-based enteric member (118 and 124 as shown) have eroded from the oral drug dosage form 100, and the top surface 116 of the first layer 112 of the erodible delay member and the bottom surface of the second layer 122 of the erodible delay member are exposed to gastrointestinal fluid. The first and second layers of the erodible delay member erode from the oral drug dosage form 100. At some time after administration to a human individual, the first and second layers of the erodible delay member (112 and 122 as shown in **FIG. 1**) have eroded away from the oral drug dosage form 100, exposing the top and bottom surfaces of the drug component 104, and the drug is released from the oral drug dosage form via the erosion of the drug component 104. In some embodiments, the drug component is broken down, and at least a portion of the drug component can be released from the oral drug dosage form and further erode to release the drug in a human individual.

Based on the teachings provided herein, any one or more components of the oral drug dosage form shown in **FIG. 1** may comprise a tracking marker (or a plurality of tracking markers) therein to provide a feature suitable for evaluating a characteristic of the oral drug dosage form following administration to an individual. For example, a tracking marker can be used to determine when and where a component begins to erode, rate of erosion, or when erosion is complete.

As shown in **FIG. 2**, a first tracking stripe is embedded in the drug component, and a first tracking loop and a second tracking loop are embedded in the non-erodible component, and wherein the top surface of the first tracking loop is in direct contact with the bottom surface of the erodible delay member. At the beginning of the administration, the first tracking stripe, the first tracking loop and the second tracking loop can be visualized in an X-ray imaging technique and their images are complete. The first tracking loop becomes shallow or deforms after erosion of the erodible delay member which indicates the drug release from the drug component. The disappearance of the first tracking stripe indicates drug release completion. The location of the second tracking loop indicates the position of the non-erodible component.

As shown in **FIG. 4**, the drug components comprise a first visible material admixed

with a drug and a first tracking stripe embedded in the non-erodible component and located between the drug components. At the beginning of the administration, the drug components and the first tracking stripe can be visualized in an X-ray imaging technique and their images are complete. The status which the drug components become shallow or deform after administration indicates the drug release from the drug components. The disappearance of the drug components indicates drug release completion. The location of the first tracking stripe indicates the position of the non-erodible component.

As shown in **FIG. 6**, a first tracking stripe and a first tracking loop are embedded in the drug component, and a second tracking loop are embedded in the non-erodible component, and wherein the top surface of the first tracking loop is in direct contact with the bottom surface of the erodible delay member. At the beginning of the administration, the first tracking stripe, the first tracking loop and the second tracking loop can be visualized in an X-ray imaging technique and their images are complete. The first tracking loop becomes shallow or deforms after erosion of the erodible delay member which indicates the drug release from the drug component. The disappearance of the first tracking stripe indicates drug release completion. The location of the second tracking loop indicates the position of the non-erodible component.

Provided herein, in some aspects, is an oral drug dosage form configured to release a drug at a desired gastrointestinal location, the oral drug dosage form comprising: a drug component comprising a first erodible material admixed with a drug and a first tracking stripe and a first tracking loop embedded in the drug component; and a delay component not admixed with the drug, the delay component comprising: a pH-based enteric member configured to erode at or above a pre-determined pH value; and an erodible delay member comprising a second erodible material, wherein the pH-based enteric member covers the erodible delay member and prevents erosion of the erodible delay member, and wherein the erodible delay member covers the drug component and prevents erosion of the drug component, and wherein one surface of the first tracking loop is in direct contact with the erodible delay member. In some embodiments, the oral drug dosage form is configured to release a drug at, near, or downstream of the ileum of an individual, such as at any one or more of the cecum, ascending colon, transverse colon, descending colon, and/ or sigmoid colon.

Provided herein, in some aspects, is an oral drug dosage form configured to release a

drug at a desired gastrointestinal location, the oral drug dosage form comprising: a drug component comprising a first erodible material admixed with a drug and a first tracking loop embedded in the drug component; and a delay component not admixed with the drug, the delay component comprising: a pH-based enteric member configured to erode at or above a pre-determined pH value; and an erodible delay member comprising a second erodible material, wherein the pH-based enteric member covers the erodible delay member and prevents erosion of the erodible delay member, and wherein the erodible delay member covers the drug component and prevents erosion of the drug component, and wherein one surface of the first tracking loop is in direct contact with the erodible delay member. In some embodiments, the oral drug dosage form is configured to release a drug at, near, or downstream of the ileum of an individual, such as at any one or more of the cecum, ascending colon, transverse colon, descending colon, and/ or sigmoid colon.

FIG. 12 provides a schematic diagram of an oral drug dosage form 200. The oral drug dosage form 200 comprises the drug component 206, and the drug component comprises a first erodible material admixed with a drug. The delay component of the oral drug dosage form 200 is not admixed with the drug and comprises: the pH-based enteric member 202 configured to erode at or above a predetermined pH value; and the erodible delay member 204 comprising a second erodible material. The pH-based enteric member 202 prevents the erosion of the erodible delay member 204, and the erodible delay member 204 prevents the erosion of the drug component 206.

Based on the teachings provided herein, any one or more components of the oral drug dosage form shown in **FIG. 12** may comprise a tracking marker (or a plurality of tracking markers) therein to provide a feature suitable for evaluating a characteristic of the oral drug dosage form following administration to an individual. For example, a tracking marker can be used to determine when and where a component begins to erode, rate of erosion, or when erosion is complete.

As shown in **FIG. 13**, a first tracking stripe and a first tracking loop are embedded in the drug component, and wherein the top surface of the first tracking loop is in direct contact with the bottom surface of the erodible delay member. At the beginning of the administration, the first tracking stripe and the first tracking loop can be visualized in an X-ray imaging technique and their images are complete. The first tracking loop becomes shallow or deforms after erosion of the erodible delay member which

indicates the drug release from the drug component. The disappearance of the first tracking stripe indicates drug release completion.

As shown in **FIG. 19**, a first tracking loop is embedded in the drug component, and wherein the top surface of the first tracking loop is in direct contact with the bottom surface of the erodible delay member. At the beginning of the administration, the first tracking loop can be visualized in an X-ray imaging technique and the image is complete. The first tracking loop becomes shallow or deforms after erosion of the erodible delay member which indicates the drug release from the drug component.

Provided herein, in some aspects, is an oral drug dosage form configured to release a drug at a desired gastrointestinal location, the oral drug dosage form comprising: a drug component comprising: a first erodible material admixed with a drug, and a body comprising: an expandable chamber configured to contain at least a portion of an expandable material, wherein the first tracking stripe is loaded in the expandable chamber, a movable component, wherein at least a portion of the movable component extends out of the body by the force provided by the expandable material; the movable component contains a drug thereon; and a second tracking stripe, wherein the second tracking stripe is coated on the movable component. In some embodiments, the oral drug dosage form is configured to release a drug in the stomach.

Provided herein, in some aspects, is an oral drug dosage form configured to release a drug at a desired gastrointestinal location, the oral drug dosage form comprising: a drug component comprising: a first erodible material admixed with a drug, and a body comprising: an expandable chamber configured to contain at least a portion of an expandable material, a movable component, wherein at least a portion of the movable component rotates around the body by the force provided by the expandable material; the movable component contains a drug thereon; and a tracking stripe, wherein the tracking stripe is coated on the movable component. In some embodiments, the oral drug dosage form is configured to release a drug in the stomach.

FIG. 21A and **FIG. 21B** provide schematic diagrams of the oral drug dosage form 300. FIGs. 21A and 21B provide an exemplary dosage form having four movable arms, where the oral drug dosage form comprises a cylinder configured to push the movable arms by the force provided by an expandable material. FIG. 21A provides a pre-administration status of the oral drug dosage form 300, where the oral drug dosage form 300 comprises a body 302 having an expandable material chamber 304 configured to

contain at least a portion of the swelling material 310. The body comprises a set of fluid inlets 308 operably connected to the expandable material chamber 304. The piston 312 is located on top of the expandable material 310. The body 302 comprises an orifice operably connected to the expandable material chamber 304, and upon expansion, the expandable material 310 pushes the piston 312, and at least a portion of the cylinder can extend out of or beyond the orifice. The oral drug dosage form 300 comprises four movable arms (the view of FIG. 21A shows the four movable arms 316, 318, 320, and 322), and at least a portion of each movable arm extends out of or further away from the body of the oral drug dosage form 300 by the force provided by the expandable material 310. Specifically, each movable arm is configured to rotate around a shaft. FIG. 21B provides a section-view image of the oral drug dosage form 300 in which the expandable material 310 has expanded and pushed the piston 312 to exert a force on each movable arm such that each movable arm moves to an extended position. In some embodiments, the components of the oral drug dosage form 300 may be produced by, such as three-dimensional printing, injection molding, ultrasonic welding, or any combination thereof, and then assembly is carried out to form the pre-administration oral drug dosage form 300. For example, in some embodiments, the body (or one or more portions thereof) is produced separately from each movable arm, and these components are subsequently assembled to form an oral drug dosage form.

Based on the teachings provided herein, any one or more components of the oral drug dosage form shown in **FIG. 21A** and **FIG. 21B** may comprise a tracking marker (or a plurality of tracking markers) therein to provide a feature suitable for evaluating a characteristic of the oral drug dosage form following administration to an individual. For example, a tracking marker can be used to determine when and where a component begins to erode, rate of erosion, or when erosion is complete or the retention time in stomach.

As shown in **FIG. 21A** and **FIG. 21B**, the first tracking stripe is loaded in the expandable chamber and there are four second tracking stripes which is coated on the four movable arms respectively. At the beginning of the administration, the first tracking stripe and the second tracking stripes can be visualized in an X-ray imaging technique. The second tracking stripes are in a compact form in a pre-administration status and in an unfolded form a post-administration status. The time of the second tracking stripes in an unfolded form indicates the retention time in stomach.

FIG. 23A to FIG. 23C provide schematic diagrams of the oral drug dosage form 400. As shown in **FIGs. 23A and 23B**, in the pre-administration status, the oral drug dosage form 400 comprises the body 402, the first movable arm 404, and the second movable arm 406 that form a capsule-like oral drug dosage form. The post-administration status of the oral drug dosage form 400 is shown in **FIG. 23C**, where the positions of the first movable arm 404 and the second movable arm 406 are located outside or further away from the body 402 of the oral drug dosage form 400, respectively. In the view of the post-administration status, the body 402 comprises a set of fluid inlets 410 thereon, and the fluid inlet 410 is operably connected to the expandable material chamber 408 that comprises at least a portion of an expandable material. In some embodiments, the components of the oral drug dosage form 400 may be produced by, such as three-dimensional printing, injection molding, ultrasonic welding, or any combination thereof, and then assembly is carried out to form the pre-administration oral drug dosage form 400. For example, in some embodiments, the body (or one or more portions thereof) is produced separately from each movable arm, and these components are subsequently assembled to form an oral drug dosage form. As shown in **FIGs. 23A to 23D**, there are three tracking stripes which is coated on the three movable arms respectively. At the beginning of the administration, the tracking stripes can be visualized in an X-ray imaging technique. The tracking stripes are in a compact form in a pre-administration status and in an unfolded form a post-administration status. The time of the tracking stripes in an unfolded form indicates the retention time in stomach. As disclosed herein, the components of an oral drug dosage form can be configured in a variety of shapes and sizes. Unless otherwise specified, references to certain shapes, sizes, and measurements reflect the oral drug dosage form prior to administration to a human individual (e.g., prior to erosion of any components of the oral drug dosage form). By the oral drug dosage form provided herein, the release initial position and/or initial time of the drug can be accurately and visually determined, so that the oral drug dosage form capable of realizing accurate delivery can be developed alone or in combination with plasma concentration data in the subsequent drug development process, and the accurate delivery of the drug is an important reference basis for increasing bioavailability, reducing side effects, improving patient compliance, reducing systemic toxicity, and improving drug stability. Further discussion of the components of the oral drug dosage form provided herein is included in the following

sections. The modular discussion of such components does not limit the scope of the present disclosure, and one of ordinary skill in the art will readily understand how to combine certain features of the following sections for use in oral drug dosage forms as taught herein.

III. Three-dimensional printing method of oral drug dosage form

In some aspects, provided herein is a method for preparing the oral drug dosage form described herein. In some embodiments, the preparation method comprises a three-dimensional (3D) printing technique that forms at least one of the components of the oral drug dosage form described herein, or a portion thereof.

In some embodiments, provided is a method of three-dimensional (3D) printing of an oral drug dosage form, which comprises allocating materials according to a layer-by-layer model of the oral drug dosage form (such as based on the thickness of the material deposited in one pass of a print head) to print the oral drug dosage form, wherein each layer of the layer-by-layer model is printed by allocating the following materials to the layer as needed: (a) a non-erodible component material for forming any portion of the non-erodible component in the layer; (b) a pH-based enteric member material for forming any portion of the pH-based enteric member in the layer; (c) an erodible delay member material for forming any portion of the erodible delay member in the layer; and (d) a drug component material for forming any portion of the drug component in the layer. In some embodiments, the method further comprises generating a layer-by-layer model of the oral drug dosage form.

In some embodiments, provided is a method of three-dimensional (3D) printing of an oral drug dosage form, which comprises allocating materials according to a layer-by-layer model of the oral drug dosage form (such as based on the thickness of the material deposited in one pass of a print head) to print the oral drug dosage form, wherein each layer of the layer-by-layer model is printed by allocating the following materials to the layer as needed: (a) a pH-based enteric member material for forming any portion of the pH-based enteric member in the layer; (b) an erodible delay member material for forming any portion of the erodible delay member in the layer; and (c) a drug component material for forming any portion of the drug component in the layer. In

some embodiments, the method further comprises generating a layer-by-layer model of the oral drug dosage form.

In some embodiments, provided is a preparation method for an oral drug dosage form, which is selected from three-dimensional (3D) printing, injection molding, ultrasonic welding, or any combination thereof for production, and then assembly is carried out to form the oral drug dosage form.

As used herein, “printing”, “three-dimensional printing”, “3D printing”, “additive manufacturing”, or equivalent terms thereof, refers to a process for producing three-dimensional objects (such as oral drug dosage forms) layer by layer using a digital design. The basic process of three-dimensional printing has been described in U.S. Pat. Nos. 5,204,055; 5,260,009; 5,340,656; 5,387,380; 5,503,785; and 5,633,021. Other U.S. patents and patent applications related to three-dimensional printing include: U.S. Pat. Nos. 5,490,962; 5,518,690; 5,869,170; 6,530,958; 6,280,771; 6,514,518; 6,471,992; 8,828,411; U.S. publication Nos. 2002/0015728; 2002/0106412; 2003/0143268; 2003/0198677; 2004/0005360. The contents of the above-mentioned U.S. patents and patent applications are hereby incorporated by reference herein in their entirety. In some embodiments, the oral drug dosage form described herein is produced using the additive manufacturing technique. In some embodiments, the oral drug dosage form described herein is produced using a layer-by-layer technique. Since 3D printing can handle a range of drug materials and can locally control composition and structure at the same time, it is well suited for manufacturing oral drug dosage forms with complex geometries and compositions according to the present disclosure.

Different 3D printing methods have been developed to manufacture in terms of raw materials, equipment, and curing. These 3D printing methods include: binder deposition (see Gibson et al., *Additive Manufacturing Technologies: 3D Printing, Rapid Prototyping, and Direct Digital Manufacturing*, 2nd edition, Springer, New York, 2015; Katstra et al., Oral dosage forms fabricated by three dimensional printing, *J Control Release*, Vol. 66, 2000; Katstra et al., Fabrication of complex oral delivery forms by three dimensional printing, master’s thesis in materials science and engineering, Massachusetts Institute of Technology, 2001; Lipson et al., *Fabricated: The New World of 3D Printing*, John Wiley & Sons, Inc., 2013; Jonathan, Karim, 3D printing in pharmaceuticals: a new tool for designing customized drug delivery systems, *Int J Pharm*, Vol. 499, 2016); material jetting (see Jonathan, Karim, 3D printing in

pharmaceutics: a new tool for designing customized drug delivery systems, *Int J Pharm*, Vol. 499, 2016); extrusion (see Gibson et al., *Additive Manufacturing Technologies: 3D Printing, Rapid Prototyping, and Direct Digital Manufacturing*, 2nd edition, Springer, New York, 2015); and photopolymerization (see Melchels et al., A review on stereolithography and its application in biomedical engineering, *Biomaterials*, Vol. 31, 2010).

In some embodiments, the oral drug dosage form described herein is 3D printed using extrusion. In some embodiments, the method of 3D printing comprises the use of the twin-screw extrusion method. In the extrusion process, the material is extruded from an automatically driven print head through a print nozzle. Unlike binder deposition, which requires a powder bed, the extrusion method can print on any substrate. Various materials can be extruded for three-dimensional printing, including the thermoplastic materials disclosed herein, pastes and colloidal suspensions, silicones, and other semi-solids. One extrusion printing method is hot melt extrusion deposition (MED), which prints material layers using materials extruded from a print head to form components of oral drug dosage forms. Another common type of extrusion printing is fused deposition modeling, which uses solid polymer filaments for printing. In the fused deposition modeling process, a gear system drives filaments into a heated nozzle component for extrusion (see Gibson et al., *Additive Manufacturing Technologies: 3D Printing, Rapid Prototyping, and Direct Digital Manufacturing*, 2nd edition, Springer, New York, 2015).

In some embodiments, the 3D printing is performed by hot melt extrusion deposition (MED). In some embodiments, the hot melt extrusion deposition technique comprises preparing materials to be allocated (such as preparing powder in a hot melt extruder) and then feeding the materials into the MED print head. The MED print head then allocates the materials to form the oral drug dosage form in an additive manner (layer-by-layer deposition). In some embodiments, the materials of the oral drug dosage form, such as the extended-release drug component, the delay component, and the non-erodible component, are allocated by different MED print heads. In some embodiments, the MED print head allocates the materials according to instructions that conform to one or more G-code files. Exemplary MED techniques are disclosed, for example, in WO2018/210183, WO2019/137333, WO2018137686, and U.S. Pat. No. 10,201,503, each of which is incorporated herein by reference in its entirety.

In some embodiments, the 3D printing is performed by fused deposition modeling (FDM). In some embodiments, the three-dimensional printing is performed by hot melt extrusion deposition or hot melt extrusion (such as FDM) in combination with 3D printing techniques. In some embodiments, the 3D printing is performed by no-filament FDM. In some embodiments, the 3D printing is performed by inkjet printing. In some embodiments, the 3D printing is performed by selective laser sintering (SLS). In some embodiments, the 3D printing is performed by stereolithography (SLA or SL). In some embodiments, the 3D printing is performed by PolyJet, MultiJet Printing (MJP) system, Perfactory, solid-state ultraviolet laser printer, Bioplotter, 3D bioprinting, rapid freeze prototyping machine, desktop system, selective deposition lamination (SDL), laminated object manufacturing (LOM), ultrasonic curing, color inkjet printing (CJP), EOSINT system, laser engineered net shape (LENS) and aerosol inkjet system, electron beam melting (EBM), laser CUSING®, selective laser melting (SLM), Phenix PXTM series, micro sintering, digital part materialization (DPM), or VX system.

In some embodiments, the 3D printing method described herein comprises a continuous feed method. In some embodiments, the 3D printing method described herein comprises a batch feed method.

The method instructions for 3D printing drug dosage forms disclosed herein may be generated in a variety of ways, including direct coding, derivation from a physical CAD model, or other means specific to the computer interface and application software of a 3D printer. The instructions may include information about the number and spatial arrangement of droplets, as well as information about general 3D printing parameters, such as droplet spacing in each linear dimension (X, Y, Z) and fluid volume or mass of each droplet. For a given set of materials, these parameters can be adjusted in order to refine the quality of the created structure. The overall resolution of the created structure depends on the powder particle size, fluid droplet size, printing parameters, and material properties.

The oral drug dosage form and the components thereof described in the present application can be printed on a commercial scale. For example, in some embodiments, the method disclosed herein can be used for 3D printing 10,000 to 100,000 units of an oral drug dosage form per hour. In some embodiments, the method disclosed herein can be used for 3D printing 10,000 to 100,000 oral drug dosage forms per hour. In some embodiments, the method disclosed herein can be used for 3D printing 10,000 to

100,000 units of dosage units per hour. In some embodiments, the method disclosed herein can be used for 3D printing 10,000 to 100,000 dosage units per hour.

The 3D printing method described herein encompasses printing materials in any order that will allow an oral drug dosage form or components thereof to be produced.

In some embodiments, the method for 3D printing comprises completely or partially designing an oral drug dosage form or components thereof on a computer system. In some embodiments, the method comprises inputting into a computer system a desired located drug release profile and/or parameters of an oral drug dosage form. In some embodiments, the method comprises providing one or more parameters to be printed, such as layer surface area, thickness, drug mass fraction, and erosion rate. In some embodiments, the method comprises providing a desired drug release profile. In some embodiments, the method comprises creating a virtual image of the article to be printed. In some embodiments, the method comprises creating a computer model containing predetermined parameters. In some embodiments, the method comprises feeding predetermined parameters to a 3D printer and printing the article according to such predetermined parameters. In some embodiments, the method comprises creating a 3D drawing of the article to be printed based on predetermined parameters, wherein the 3D drawing is created on a computer system. In some embodiments, the method comprises converting (such as slicing) the 3D drawing into 3D printing code (e.g., G-code). In some embodiments, the method comprises executing 3D printing code using a computer system to print according to the method described herein.

In some aspects, provided herein is a method for designing an oral drug dosage form configured to release a drug at a desired gastrointestinal location in an individual. In some embodiments, the method comprises using one or more tracking strips (such as erodible tracking strips) embedded in one or more components of the oral drug dosage form such that the location and status of the oral drug dosage form or components thereof can be monitored. For example, in some embodiments, the tracking strip may be detectable via an imaging technique (such as an X-ray technique). In some embodiments, the tracking strip is located in the non-erodible component of the oral drug dosage form. In some embodiments, the tracking strip is located in the pH-based enteric member of the oral drug dosage form. In some embodiments, the tracking strip is located in the erodible delay member of the oral drug dosage form. In some embodiments, the tracking strip is located in the drug component of the oral drug dosage

form. In some embodiments, the drug component comprises a tracking marker material admixed with the drug.

In some aspects, provided herein is a method of making/ designing comprising making a precursor oral drug dosage form using the tracking markers and then removing the tracking markers to make/ design the oral drug dosage form.

The tracking marker material contains features appropriate to the imaging technique used. For example, in some embodiments, the tracking strip comprises barium sulfate. In some embodiments, the imaging includes X-ray imaging.

The tracking marker (e.g., the tracking strip) described herein can be produced in any shape (such as a loop, strip, layer, or block) and in any component of the oral drug dosage form, such as by the three-dimensional printing. In some embodiments, a designed oral drug dosage form comprising one or more tracking markers (such as a tracking strip) can be produced without one or more of these tracking markers. An oral drug dosage form described herein having the tracking markers removed therefrom. Such an oral drug dosage form with the removal of the tracking marker may retain the original size of its components such that the removal of the tracking marker does not affect the drug release and/or subsequent development of the oral drug dosage form. In some embodiments, the space of the tracking marker is filled with a non-drug containing material such that the removal of the tracking marker does not affect the drug release and/or subsequent development of the oral drug dosage form. In some embodiments, such an oral drug dosage form with the removal of the tracking marker may change the original size of its components such that the removal of the tracking marker does not affect the drug release and/or subsequent development of the oral drug dosage form. The tracking marker (such as a tracking strip) may comprise a variety of materials, and in some embodiments, these materials are customized for the components of the oral drug dosage form in which the tracking marker is embedded. In some embodiments, the tracking marker (such as a tracking strip) comprises an erodible material. In some embodiments, the tracking marker (such as a tracking strip) comprises a non-erodible material. In some embodiments, the visible material in the tracking marker is not admixed with a drug.

In some embodiments, the method for producing the oral drug dosage form described

herein comprises a combination of a three-dimensional (3D) printing technique and another method, e.g., a combination of injection molding and 3D printing. In some embodiments, the method for producing further comprises an injection molding technique. In some embodiments, the method for producing further comprises an ultrasonic welding method. In some embodiments, the 3D printing technique, the injection molding technique, and the ultrasonic welding method may be used alone or in any combination.

In some embodiments, the 3D printing method described herein comprises three steps including physical premix, hot melt extrusion, and 3D printing. Physical premix involves physically mixing an erodible material and a drug core material separately. The erodible material is formed by mixing an erodible polymer and a plasticizer, and additives may be added in a preferable scheme. The drug core material is formed by mixing an active pharmaceutical ingredient, a plasticizer, and an erodible polymer material. The tracking marker material may be formed by mixing a visible material and an erodible polymer material or a non-erodible polymer material or a drug core material. The drug core material and the tracking marker material are separately melted uniformly to prepare an intermediate or are directly sent to a print head of a 3D printer. The different compositions of the tablet are alternately and sequentially extruded from respective print nozzles on the 3D printer according to preset printing instructions. Taking the 3D printing of a drug comprising a delay layer as an example, the delay layer print head prints out the bottom of the tablet, and then the delay layer print head and the drug core print head work together to construct the middle part of the tablet. The tracking marker print head prints the tracking marker in a preset shape. Finally, the top of the tablet is printed out by the delay print head.

IV. Method for verifying release effect of oral drug dosage form

In some aspects, provided herein is a method for verifying the release effect of an oral drug dosage form comprising a tracking marker and a drug component, and the method comprises: (a) administering a drug; (b) imaging to obtain the location and status of the tracking marker; (c) determining the drug release condition based on the location and the status.

In some embodiments, the process of imaging comprises taking at least two shots or images of the individual after administration, with an interval of at least 30 min between the two shots or images. In some embodiments, the process of imaging comprises taking at least three shots or images of the individual within 12 h after administration. In some embodiments, the process of imaging comprises taking no more than six shots or images of the individual within 12 h after administration. In some embodiments, the process of imaging comprises taking no more than 5 shots or images of the individual within 24 h after administration.

In some embodiments, the verification method further comprises obtaining (such as measuring) one or more pharmacokinetic (PK) parameters associated with the drug after administration of the oral drug dosage form to the individual. PK parameters are well known in the art and include, for example, T_{det} , T_{max} , C_{max} , and AUC. In some embodiments, the verification method further comprises identifying the relationship between one or more PK parameters and the location and status information of the first tracking strip, such as the difference between T_{det} and the time at which the first tracking strip embedded in or located near the drug component begins to erode (as determined using imaging) within about 1 h. In some embodiments, the verification method further comprises adjusting the drug component and/or the delay component or portions thereof based on the relationship between one or more PK parameters and the location and status information of the first tracking strip, such as the difference between T_{det} and the time at which the first tracking strip embedded in or located near the drug component begins to erode (as determined using imaging) within about 1 h.

In some embodiments, the verification method further comprises obtaining the angle between the tracking markers, relative position of the tracking markers, or number after administering the oral drug dosage form to the individual.

V. Device for testing release effect of oral drug dosage form

In some aspects, provided herein is a device for testing the release effect of an oral drug dosage form, which comprises a non-erodible component, a delay component, a first tracking marker, and/or a second tracking marker, wherein whether the drug achieves a preset effect or not is determined according to the imaging locations and status of the

first tracking marker and the second tracking marker.

In other aspects, provided herein is a device for testing the release effect of an oral drug dosage form, which comprises a delay component, a first tracking marker, and/or a second tracking marker, wherein whether the drug achieves a preset effect or not is determined according to the imaging locations and status of the first tracking marker and the second tracking marker.

In other aspects, provided herein is a device for testing the release effect of an oral drug dosage form, which comprises a body, a movable component, a first tracking marker, and/or a second tracking marker, wherein whether the drug achieves a preset effect or not is determined according to the imaging locations and status of the first tracking marker and the second tracking marker.

The device for testing the release effect of an oral drug dosage form provided herein can be used to test any oral drug dosage form that requires targeted drug delivery. In some embodiments, the oral drug dosage form that is located at or near the colon of an individual is tested. In some embodiments, the oral drug dosage form that is located at the stomach is tested. In some embodiments, the oral drug dosage form is tested for gastric retention time.

The device for testing the release effect of an oral drug dosage form provided herein can be used to test the retention time of a drug at any location in an animal. In some embodiments, the retention time in the stomach is tested. In some embodiments, the object of the test is a human.

The imaging location and status of the tracking marker in the method for verifying the release effect of an oral drug dosage form, the device for testing the release effect of an oral drug dosage form, and the method for designing an oral drug dosage form configured to release a drug at a desired gastrointestinal location in an individual provided herein may be accomplished by artificial intelligence or image recognition. The image recognition may be based on the image data obtained in the foregoing methods, and the image data is labeled, that is, the objects in the image are classified and described. More specifically, the image data can be segmented to obtain a target for the tracking marker. The labeled data is trained by using a machine learning algorithm to generate an image learning analysis model. The trained model is applied to a new image to determine whether the oral drug dosage form achieves the release

effect or not according to the image information. The compositions and proportions of the drug component, the delay or erodible component and/or the non-erodible component of the oral drug dosage form are fitted according to the release effect, and the information is input into a 3D drug printer until an updated oral drug dosage form is obtained.

Based on the test results, the release of the drug from the oral drug dosage form is adjusted. In some embodiments, the adjustment comprises adjusting the delay component or a portion thereof based on the location and the status of the first erodible tracking strip as being in the status of release earlier than desired to increase the delay in the release of the drug from the oral drug dosage form. In some embodiments, the adjustment comprises adjusting the delay component or a portion thereof based on the location and the status of the first erodible tracking strip as being in the status of release later than desired to decrease the delay in the release of the drug from the oral drug dosage form. In some embodiments, the adjustment comprises the retention time of the oral drug dosage form that is shorter than the desired one to increase the retention time of the oral drug dosage form. In some embodiments, the adjustment comprises the retention time of the oral drug dosage form that is longer than the desired one to decrease the retention time of the oral drug dosage form. Techniques for adjusting an oral drug dosage form to increase or decrease drug release from the oral drug dosage form or to increase or decrease the retention time of the oral drug dosage form are known in the art and include, for example, adjusting thickness, surface area, and material properties. Adjusting techniques are described in U.S. Pat. No. 10,350,822, which is hereby incorporated by reference in its entirety.

In other aspects, provided herein is a device for testing the erosion effect of a delay component comprised in an oral drug dosage form, comprising a compartment formed by a first erodible material; a delay component comprising the first erodible material, wherein the delay component covers the compartment, and a first tracking marker comprising: a second erodible material admixed with a first visible material, wherein the first tracking marker is embedded in the delay component. The status of the first tracking marker which deforms or disappears indicates the erosion effect of the delay component. The deformation of the first tracking marker indicates the beginning of the erosion of the delay component and the disappearance of the first tracking marker indicates the ending of the erosion of the delay component. The tracking images

indicate whether the erodible material starts to or finish to erode at a certain location without loading a drug through the device provided herein.

Examples

Example 1

This example illustrates the design, manufacture, and testing of the oral drug dosage form described herein. The oral drug dosage form described herein is configured for drug release between the ileum-cecum region to the colon.

FIG. 1 provides a schematic diagram of an oral drug dosage form. To understand the erosion of the components of the oral drug dosage form, as shown in **FIG. 2**, various tracking strips that can be seen on an X-ray image of a patient were included. The final form of the oral drug dosage form will not comprise such a tracking strip, and such a feature part was only needed during the design stage to ensure proper targeted drug delivery. The oral drug dosage form was 3D printed using a MED 3D printing system.

As shown in **FIG. 2**, the oral drug dosage form comprises: a non-erodible component that is not admixed with a drug; a drug component comprising a first erodible material admixed with the drug; and a delay component that is not admixed with the drug and comprises two layers of a pH-based enteric member and two layers of an erodible delay member. The pH-based enteric member is configured to erode at or above a predetermined pH value, and the erodible delay member comprises a second erodible material. Each layer of the pH-based enteric member and the non-erodible component prevent the erosion of the corresponding layer of the erodible delay member, and the erodible delay member and the non-erodible component prevent the erosion of the drug component. After administration, the layer of the pH-based enteric member erodes, exposing the layer of the erodible delay member to the gastrointestinal fluid, such that the layer of the erodible delay member subsequently begins to erode. The layer of the erodible delay member erodes, exposing the surface of the drug component, such that the surface of the drug component erodes and the drug is released from the oral drug dosage form. As shown in **FIG. 2**, the oral drug dosage form may comprise a tracking strip. Such a tracking strip is used to develop and optimize an oral drug dosage form. For example, after administration, imaging an individual (such as using X-rays) can be

used to determine the location of the erosion of the drug dosage form. The disclosure provided herein also encompasses oral drug dosage forms that do not have one or more tracking strips. For example, these tracking strips may not be needed after the development and optimization of an oral drug dosage form. **Table 1A** and **Table 1B** provide detailed information for the oral drug dosage form shown in **FIG. 2**.

Table 1A: Size of oral drug dosage form shown in **FIG. 2**

	Width (mm)	Length (mm)	Height (mm)
Non-erodible component	W1=8.8	L1=13.6	H1=3.2
Layer of pH-based enteric member (both layers having the same size)	W2=8.0	L2=12.8	H2=0.6
Layer of erodible delay member (both layers having the same size)	W3=7.2	L3=12.0	H3=0.6
Drug component	W4=4.0	L4=8.8	H4=0.8
Tracking strip	W5=6.4, W8=4.8	L5=11.2, L8=9.6	H5=0.4
Tracking strip	W6=0.8	L6=5.6	H6=0.4
Tracking strip	W7=8.0, W9=7.2	L7=12.8, L9=12.0	H7=0.4

In some embodiments, the non-erodible component comprises ethyl cellulose (EC), dibutyl sebacate (DBS), and titanium dioxide (TiO₂). In some embodiments, the pH-based enteric member comprises vinyl acetate copolymer (VA64), poly(methacrylic acid-co-ethyl acrylate), and triethyl citrate (TEC). In some embodiments, the erodible delay member comprises hydroxypropyl cellulose, dicalcium phosphate (CaHPO₄), and TEC. In some embodiments, the drug component comprises the drug tofacitinib citrate, VA64, and TEC. In some embodiments, the tracking strip comprises barium sulfate (BaSO₄), VA64, and TEC. In some embodiments, the content of barium sulfate in the tracking strip is 40.03% by weight of the tracking strip.

In some embodiments, the oral drug dosage form of **Table 1A** comprises the weight percentages (w/w%) and total weight of the components listed in **Table 1B**.

Table 1B: Components of oral drug dosage form shown in **FIG. 2**

Component	Composition (w/w%)	Unit (mg/tablet)
Poly(methacrylic acid-co-ethyl acrylate)	5.92	21
Vinyl acetate copolymer	24.34	86.35
Triethyl citrate	10.63	37.72
Hydroxypropyl cellulose	23.45	83.2
Anhydrous dicalcium phosphate (CaHPO ₄)	2.93	10.4
Tofacitinib citrate	2.50	8.88
Ethyl cellulose	23.11	82
Dibutyl sebacate	5.02	17.8
Titanium dioxide	0.06	0.2
Barium sulfate	2.04	7.2
Total weight of tablet	100	354.75

In vitro dissolution rates of the oral drug dosage form were tested using a dissolution technique that simulates gastric and intestinal conditions. The dissolution rates were measured according to the methods provided in the FDA dissolution method database. Briefly, the oral drug dosage form was placed in 250 mL of FaSSGF (fasting state simulated gastric fluid) for 30 min (0.5 h) in a drug dissolution device USP II (paddle method) at 100 rpm. The oral drug dosage form was then transferred to 250 mL of FaSSIF (fasting state simulated intestinal fluid) in a drug dissolution device USP II (paddle method) at 100 rpm. The percentage of the accumulative dissolution was measured at intervals until the erodible material was completely dissolved.

As shown in **FIG. 3**, no drug was detected after 30 min in FaSSGF. In FaSSIF, tofacitinib was not released from the oral drug dosage form until 4 h after the simulated administration, and the complete release of tofacitinib occurred about 8 h after the simulated administration. **FIG. 3** also provides a schematic diagram of the status of the oral drug dosage form and the tracking strip during the experiment. For the time points

of the dissolution profile in **FIG. 3**, the data points are based on the mean of three replicates, and the standard deviation is provided using an error bar.

The oral drug dosage form will be subjected to *in vivo* pharmacokinetic studies in animal and human subjects. After administration, the oral drug dosage form will be tracked using X-ray scanning. The onset of drug release is characterized by the disappearance of the tracking strip in the erodible delay member, and the completion of the release of the drug component from the oral drug dosage form is characterized by the disappearance of the tracking strip in the drug component. Once the location of drug release is confirmed in the ileum-cecum region or the ascending colon, the tracking strip will no longer be necessary in future clinical trials.

Example 2

This example illustrates the design, manufacture, and testing of the oral drug dosage form described herein. The oral drug dosage form described herein is configured for drug release between the ileum-cecum region to the colon.

FIG. 1 provides a schematic diagram of an oral drug dosage form. To understand the erosion of the components of the oral drug dosage form, as shown in **FIG. 4**, various tracking strips that can be seen on an X-ray image of a patient were included. The final form of the oral drug dosage form will not comprise such a tracking strip, and such a feature part was only needed during the design stage to ensure proper targeted drug delivery. The oral drug dosage form was 3D printed using a MED 3D printing system.

As shown in **FIG. 4**, the oral drug dosage form comprises: a non-erodible component that is not admixed with a drug; a drug component comprising a first erodible material admixed with the drug; and a delay component that is not admixed with the drug and comprises two layers of a pH-based enteric member and three layers of an erodible delay member. The pH-based enteric member is configured to erode at or above a predetermined pH value, and the erodible delay member comprises a second erodible material. Each layer of the pH-based enteric member and the non-erodible component prevent the erosion of the corresponding layer of the erodible delay member, and the erodible delay member and the non-erodible component prevent the erosion of the drug component. After administration, the layer of the pH-based enteric member erodes,

exposing two layers of the erodible delay member to the gastrointestinal fluid, such that the two layers of the erodible delay member subsequently begins to erode. One of the layers of the erodible delay member erodes, exposing one surface of the drug component. One of the layers of the erodible delay member erodes, exposing another layer (VA64 layer) of the erodible delay member on the side of the drug component. After the VA64 layer of the erodible delay member erodes, the other surface of the drug component is exposed. The exposed surfaces of the drug component erode to release the drug from the oral drug dosage form. As shown in FIG. 4, the oral drug dosage form may comprise a tracking strip. Such a tracking strip is used to develop and optimize an oral drug dosage form. For example, after administration, imaging an individual (such as using X-rays) can be used to determine the location of the erosion of certain aspects of the drug dosage form. The disclosure provided herein also encompasses oral drug dosage forms that do not have one or more tracking strips. For example, these tracking strips may not be needed after the development and optimization of an oral drug dosage form. **Table 2A** and **Table 2B** provide detailed information for the oral drug dosage form shown in **FIG. 4**.

Table 2A: Size of oral drug dosage form shown in **FIG. 4**

	Width (mm)	Length (mm)	Height (mm)
Non-erodible component	W1=8.8	L1=12.8	H1=4.0
Layer of pH-based enteric member (both layers having the same size)	W2=8.0	L2=12.0	H2=0.6
Layer of erodible delay member (both layers having the same size)	W6=7.2	L6=11.2	H6=0.6
VA64 layer of erodible delay member	W3=6.4	L3=10.8	H3=0.4
Drug component	W4=1.7	L4=9.7	H4=1.2
Tracking strip	W5=0.8	L5=8.0	H5=0.8

In some embodiments, the non-erodible component comprises ethyl cellulose (EC), dibutyl sebacate (DBS), and titanium dioxide (TiO₂). In some embodiments, the pH-based enteric member comprises vinyl acetate copolymer (VA64), poly(methacrylic acid-co-ethyl acrylate), and triethyl citrate (TEC). In some embodiments, the erodible

delay member comprises hydroxypropyl cellulose, anhydrous dicalcium phosphate (CaHPO₄), and TEC. In some embodiments, the erodible delay member (such as a VA64 layer) comprises VA64 and polyethylene glycol (PEG, e.g., PEG4000). In some embodiments, the drug component comprises the drug tofacitinib citrate, barium sulfate (BaSO₄), and PEG (such as PEG20000). In some embodiments, the content of barium sulfate in the drug component is 54.5% by weight of the drug component. In some embodiments, the tracking strip comprises barium sulfate (BaSO₄) and PEG (such as PEG20000). In some embodiments, the content of barium sulfate in the tracking strip is 60.3% by weight of the tracking strip.

In some embodiments, the oral drug dosage form of **Table 2A** comprises the weight percentages (w/w%) and total weight of the components listed in **Table 2B**.

Table 2B: Components of oral drug dosage form shown in **FIG. 4**

Component	Composition (w/w%)	Unit (mg/tablet)
Poly(methacrylic acid-co-ethyl acrylate)	4.96	20
Vinyl acetate copolymer	19.11	77
Polyethylene glycol 400	0.74	3
Polyethylene glycol 20000	2.47	9.97
Triethyl citrate	7.34	29.6
Hydroxypropyl cellulose	19.06	76.8
Anhydrous dicalcium phosphate (CaHPO ₄)	2.38	9.6
Tofacitinib citrate	0.52	2.09
Ethyl cellulose	33.75	136
Dibutyl sebacate	5.88	23.68
Titanium dioxide	0.08	0.32

Barium sulfate	3.71	14.94
Total weight of tablet	100	403

In vitro dissolution rates of the oral drug dosage form were tested using a dissolution technique that simulates gastric and intestinal conditions. The dissolution rates were measured according to the methods provided in the FDA dissolution method database. Briefly, the oral drug dosage form was placed in 250 mL of FaSSGF (fasting state simulated gastric fluid) for 30 min (0.5 h) in a drug dissolution device USP II (paddle method) at 100 rpm. The oral drug dosage form was then transferred to 250 mL of FaSSIF (fasting state simulated intestinal fluid) in a drug dissolution device USP II (paddle method) at 100 rpm. The percentage of the accumulative dissolution was measured at intervals until the erodible material was completely dissolved.

As shown in **FIG. 5**, no drug was detected after 30 min in FaSSGF. In FaSSIF, tofacitinib was not released from the oral drug dosage form until 4.5 h after the simulated administration, and the complete release of tofacitinib occurred about 9.5 h after the simulated administration. **FIG. 5** also provides a schematic diagram of the status of the oral drug dosage form and the tracking strip during the experiment. The data in **FIG. 5** represent four replicates and the results are the mean $\pm$ standard deviation among these replicates.

Example 3

This example illustrates the design, manufacture, and testing of the oral drug dosage form described herein. The oral drug dosage form described herein is configured for drug release between the ileum-cecum region to the colon.

FIG. 1 provides a schematic diagram of an oral drug dosage form. To understand the erosion of the components of the oral drug dosage form, as shown in **FIG. 6**, various tracking strips that can be seen on an X-ray image of a patient were included. The final form of the oral drug dosage form will not comprise such a tracking strip, and such a feature part was only needed during the design stage to ensure proper targeted drug delivery. The oral drug dosage form was 3D printed using a MED 3D printing system.

As shown in **FIG. 6**, the oral drug dosage form comprises: a non-erodible component that is not admixed with a drug; a drug component comprising a first erodible material admixed with the drug; and a delay component that is not admixed with the drug and comprises two layers of a pH-based enteric member and two layers of an erodible delay member. The pH-based enteric member is configured to erode at or above a predetermined pH value, and the erodible delay member comprises a second erodible material. Each layer of the pH-based enteric member and the non-erodible component prevent the erosion of the corresponding layer of the erodible delay member, and the erodible delay member and the non-erodible component prevent the erosion of the drug component. After administration, the layer of the pH-based enteric member erodes, exposing the layer of the erodible delay member to the gastrointestinal fluid, such that the layer of the erodible delay member subsequently begins to erode. The layer of the erodible delay member erodes, exposing the surface of the drug component, such that the surface of the drug component erodes and the drug is released from the oral drug dosage form. As shown in **FIG. 6**, the oral drug dosage form may comprise a tracking strip. Such a tracking strip is used to develop and optimize an oral drug dosage form. For example, after administration, imaging an individual (such as using X-rays) can be used to determine the location of the erosion of certain aspects of the drug dosage form. The disclosure provided herein also encompasses oral drug dosage forms that do not have one or more tracking strips. For example, these tracking strips may not be needed after the development and optimization of an oral drug dosage form.

Table 3A provides one kind of size of the oral drug dosage form shown in **FIG. 6**.

Table 3A: Size of oral drug dosage form shown in **FIG. 6**

	Width (mm)	Length (mm)	Thickness (mm)
Non-erodible component	W1=8.0	L1=12.8	T1=3.8
Layer of pH-based enteric member (both layers having the same size)	W2=5.6	L2=10.4	T2=0.6
Layer of erodible delay member (both layers having the same size)	W3=4.8	L3=9.6	T3=0.8
Drug component	W4=4.0	L4=8.8	T4=1.0
Tracking loop	W5=3.2, W5'=0.4	L5=8.0	T5=0.2

Tracking strip	W6=0.8	L6=5.6	T6=0.6
Tracking loop	W7=7.2, W7'=0.4	L7=12.0	T7=0.4

In some embodiments, the non-erodible component comprises ethyl cellulose (EC), dibutyl sebacate (DBS), and titanium dioxide (TiO₂). In some embodiments, the pH-based enteric member comprises vinyl acetate copolymer (VA64), poly(methacrylic acid-co-ethyl acrylate), triethyl citrate (TEC), and titanium dioxide (TiO₂). In some embodiments, the erodible delay member comprises hydroxypropyl cellulose, TEC, vitamin E polyethylene glycol 1000 succinate (TPGS), and TiO₂. In some embodiments, the drug component comprises the drug tofacitinib citrate, VA64, and TEC. In some embodiments, the tracking strip or tracking loop comprises barium sulfate (BaSO₄), VA64, and TEC. In some embodiments, the content of barium sulfate in the tracking strip or tracking loop is 50.5% by weight of the tracking strip or tracking loop.

In some embodiments, the oral drug dosage form of **Table 3A** comprises the weight percentages (w/w%) and total weight of the components listed in **Table 3B**.

Table 3B: Components of oral drug dosage form shown in **FIG. 6**

Component	Composition (w/w%)	Unit (mg/tablet)
Poly(methacrylic acid-co-ethyl acrylate)	3.47	12.8
Vitamin E polyethylene glycol 1000 succinate (TPGS)	1.00	3.70
Vinyl acetate copolymer	16.79	62.01
Triethyl citrate	8.20	30.27
Hydroxypropyl cellulose	15.97	58.97
Tofacitinib citrate	2.40	8.88
Ethyl cellulose	41.06	151.73

Dibutyl sebacate	8.92	32.93
Titanium dioxide	0.18	0.65
Barium sulfate	2.01	7.42
Total weight of tablet	100	369.36

Table 4A also provides another kind of size of the oral drug dosage form shown in **FIG. 6**.

Table 4A: Size of oral drug dosage form shown in **FIG. 6**

	Width (mm)	Length (mm)	Thickness (mm)
Non-erodible component	W1=8.0	L1=12.8	T1=3.83
Layer of pH-based enteric member (both layers having matching sizes)	W2=5.6	L2=10.4	T2=0.6
Layers of erodible delay member (both layers having matching sizes)	W3=4.8	L3=9.6	T3=0.84
Drug component	W4=4.0	L4=8.8	T4=0.95
Tracking loop	W5=3.2, W5'=0.4	L5=8.0	T5=0.19
Tracking strip	W6=0.8	L6=5.6	T6=0.57
Tracking loop	W7=7.2, W7'=0.4	L7=12.0	T7=0.42

In some embodiments, the non-erodible component comprises ethyl cellulose (EC), dibutyl sebacate (DBS), and titanium dioxide (TiO₂). In some embodiments, the pH-based enteric member comprises vinyl acetate copolymer (VA64), poly(methacrylic acid-co-ethyl acrylate), triethyl citrate (TEC), and titanium dioxide (TiO₂). In some embodiments, the erodible delay member comprises hydroxypropyl cellulose, TEC, vitamin E polyethylene glycol 1000 succinate (TPGS), and TiO₂. In some embodiments, the drug component comprises the drug tofacitinib citrate, VA64, and TEC. In some embodiments, the tracking strip or tracking loop comprises barium sulfate (BaSO₄), VA64, and TEC. In some embodiments, the content of barium sulfate

in the tracking strip or tracking loop is 50.3% by weight of the tracking strip or tracking loop.

In some embodiments, the oral drug dosage form of **Table 4A** comprises the weight percentages (w/w%) and total weight of the components listed in **Table 4B**.

Table 4B: Components of oral drug dosage form shown in **FIG. 6**

Component	Composition (w/w%)	Unit (mg/tablet)
Poly(methacrylic acid-co-ethyl acrylate)	3.42	12.8
Vitamin E polyethylene glycol 1000 succinate (TPGS)	1.04	3.88
Vinyl acetate copolymer	15.73	58.90
Triethyl citrate	8.04	30.08
Hydroxypropyl cellulose	16.54	61.92
Tofacitinib citrate	2.37	8.88
Ethyl cellulose	40.85	152.93
Dibutyl sebacate	8.87	33.20
Titanium dioxide	0.18	0.66
Barium sulfate	2.96	11.10
Total weight of tablet	100	374.35

In vitro dissolution rates of the oral drug dosage form were tested using a dissolution technique that simulates gastric and intestinal conditions. The dissolution rates were measured according to the methods provided in the FDA dissolution method database. Briefly, the oral drug dosage form was placed in 250 mL of FaSSGF (fasting state simulated gastric fluid) for 30 min (0.5 h) in a drug dissolution device USP II (paddle method) at 100 rpm. The oral drug dosage form was then transferred to 250 mL of FaSSIF (fasting state simulated intestinal fluid) in a drug dissolution device USP II (paddle method) at 100 rpm. The percentage of the accumulative dissolution was

measured at intervals until the erodible material was completely dissolved.

As shown in **FIG. 7**, no drug was detected after 30 min in FaSSGF. In FaSSIF, tofacitinib was not released from the oral drug dosage form until 5 h after the simulated administration. **FIG. 7** also provides a schematic diagram of the status of the oral drug dosage form and the tracking strip during the experiment. The data in **FIG. 7** represent three replicates and the results are the mean $\pm$ standard deviation among these replicates.

These *in vitro* results show that the drug release from the oral drug dosage form can be effectively delayed when evaluated in a biologically relevant medium with a reasonable volume of 250 mL in each of the simulated fluids, suggesting that the prototype tablet has the potential for colon-targeted delivery, with the thickness-delay time relationship of the layers used for optimization.

Example 4

PK and X-ray studies were performed using beagle dogs. Beagle dogs (age: 15 months to 16 months; body weight: 7.9 kg to 8.8 kg) were purchased from Beijing Marshall Bioresources, Beijing, China. Each animal was individually housed in a stainless-steel cage in a controlled environment (temperature 16 °C to 26 °C, humidity 40% to 70%, 12 h light/12 h dark cycle). Each dog was marked with an ear tattoo. Prior to administration, the dogs were transferred to the facility of Suzhou Chuxin Pet Hospital Co., Ltd. and acclimatized for 2 days, where animal experiments and rearing were performed.

Prior to oral administration, the dogs were deprived of food and given pentagastrin via injection to adjust the stomach to low pH, thereby simulating the pH conditions in the human stomach in fasting conditions. For animals orally receiving one oral drug dosage form, X-ray scans were recorded, and X-ray images were collected until the completion of drug release as indicated by the disappearance of barium sulfate in the oral drug dosage form. Also, blood samples were collected from the jugular veins of the beagle dogs. For animals orally receiving the reference drug Xeljanz[®] XR, only blood samples were collected from the jugular veins of the beagle dogs, and PK parameters were calculated. The X-ray images were used to assess the location, transit time, and release

properties in the gastrointestinal tract at different time points. **Table 5** provides the PK results.

Table 5: PK parameters measured from beagle dogs administered oral drug dosage forms comprising tofacitinib

PK parameter		Reference (n = 6)	*Table 2A and Table 2B (n = 2)	*Table 3A and Table 3B (n = 2)	*Table 4A and Table 4B (n = 6)
[#] T _{det}	h	NA	7(7)	6.75 (6.0-7.5)	8 (6.0-24.0)
Median (range)					
[#] T _{max}	h	3 (2.0-4.0)	9(9)	7 (6.0-8.0)	9 (6.5-24.0)
Median (range)					
C _{max} (mean ± SD)	ng/mL	74.4 ± 21.5	7.5	45.0	22.3±14.8
AUC _{0-t} (mean ± SD)	ng*h/mL	242±55.9	33.8	150	98.7±81.3
AUC _{0-inf} (mean ± SD)	ng*h/mL	252±56.3	36.6	155	121±75.6
C _{max} /dose (mean ± SD)	kg*ng/mL/mg	56.4±16.0	72.1	107.9	33.9±22.9
AUC _{0-t} /dose (mean ± SD)	h*kg*ng/mL/mg	183±42.5	327.5	360	150±125
AUC _{0-inf} /dose (mean ± SD)	h*kg*ng/mL/mg	191±42.4	354.7	372	184±116

Note: [#]T_{det} and T_{max} show the median value instead of the mean and show the range instead of SD.

NA: not applicable.

*Since the number of dogs in tables 2 and 3 was two, PK parameters were mean values rather than SD values.

FIG. 8A and **FIG. 8B** provide the PK profiles for the oral drug dosage forms tested. **FIG. 9 to FIG. 11** provide X-ray images. Each X-ray image indicates the onset of drug release and the completion of drug release.

Example 5

This example illustrates the design, manufacture, and testing of the oral drug dosage form described herein. The oral drug dosage form described herein is configured for drug release between the ileum-cecum region to the colon.

FIG. 12 provides a schematic diagram of an oral drug dosage form. To understand the erosion of the components of the oral drug dosage form, as shown in **FIG. 13**, various tracking strips that can be seen on an X-ray image of a patient were included. The final form of the oral drug dosage form will not comprise such a tracking strip, and such a feature part was only needed during the design stage to ensure proper targeted drug delivery. The oral drug dosage form was 3D printed using a MED 3D printing system.

As shown in **FIG. 13**, the oral drug dosage form comprises: a drug component comprising a first erodible material admixed with a drug; and a delay component that is not admixed with the drug and comprises a pH-based enteric member and an erodible delay member. The pH-based enteric member is configured to erode at or above a predetermined pH value, and the erodible delay member comprises a second erodible material. The pH-based enteric member prevents the erosion of the erodible delay member, and the erodible delay member prevents the erosion of the drug component. After administration, the pH-based enteric member erodes, exposing the erodible delay member to the gastrointestinal fluid, such that the erodible delay member subsequently begins to erode. The erodible delay member erodes, exposing the surface of the drug component, such that the surface of the drug component erodes and the drug is released from the oral drug dosage form. As shown in **FIG. 13**, the oral drug dosage form may comprise a tracking strip. Such a tracking strip is used to develop and optimize an oral drug dosage form. For example, after administration, imaging an individual (such as using X-rays) can be used to determine the location of the erosion of the drug dosage form. The disclosure provided herein also encompasses oral drug dosage forms that do not have one or more tracking strips. For example, these tracking strips may not be needed after the development and optimization of an oral drug dosage form.

Table 6A and **Table 6B** provide detailed information for the oral drug dosage form shown in **FIG. 13**. H1 was 2.38 mm, and H2 was 1.92 mm.

Table 6A: Size of oral drug dosage form shown in **FIG. 13**

	Width (mm)	Length (mm)	Thickness (mm)
pH-based enteric member	W1=7.6	L1=15.0	T1=4.3
Erodible delay member	W2=6.8	L2=14.2	T2=4.0
Drug component	W3=3.2	L3=10.6	T3=0.92
Tracking loop	W4=3.2, W4'=0.4	L4=10.6	T4=0.23
Tracking strip	W5=0.8	L5=8.2	T5=0.46

In some embodiments, the pH-based enteric member comprises hydroxypropyl methylcellulose acetate succinate (HPMCAS), triethyl citrate (TEC), and titanium dioxide (TiO₂). In some embodiments, the erodible delay member comprises hydroxypropyl cellulose (HPC), TEC, vitamin E polyethylene glycol 1000 succinate (TPGS), and TiO₂. In some embodiments, the drug component comprises the drug tofacitinib citrate, VA64, and TEC. In some embodiments, the tracking strip or tracking loop comprises barium sulfate (BaSO₄), VA64, and TEC. In some embodiments, the content of barium sulfate in the tracking strip or tracking loop is 70.12% by weight of the tracking strip or tracking loop.

In some embodiments, the oral drug dosage form of **Table 6A** comprises the weight percentages (w/w%) and total weight of the components listed in **Table 6B**.

Table 6B: Components of oral drug dosage form shown in **FIG. 13**

Component	Composition (w/w%)	Unit (mg/tablet)
Hydroxypropyl methylcellulose acetate succinate (HPMCAS)	17.13	87.78
Vitamin E polyethylene glycol 1000 succinate (TPGS)	3.54	18.20
Vinyl acetate copolymer	3.54	18.12
Triethyl citrate	15.93	81.61
Hydroxypropyl cellulose	56.69	290.47
Tofacitinib citrate	1.73	8.88
Titanium dioxide	0.19	0.95
Barium sulfate	1.25	6.40

Total weight of tablet	100	512.41
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Table 7A also provides another kind of size of the oral drug dosage form shown in **FIG. 13**. H1 was 1.59 mm, and H2 was 1.13 mm.

Table 7A: Size of oral drug dosage form shown in **FIG. 13**

	Width (mm)	Length (mm)	Thickness (mm)
pH-based enteric member	W1=7.6	L1=15.0	T1=2.72
Erodible delay member	W2=6.8	L2=14.2	T2=2.42
Drug component	W3=3.2	L3=10.6	T3=0.92
Tracking loop	W4=3.2, W4'=0.4	L4=10.6	T4=0.23
Tracking strip	W5=0.8	L5=8.2	T5=0.46

In some embodiments, the pH-based enteric member comprises hydroxypropyl methylcellulose acetate succinate (HPMCAS), triethyl citrate (TEC), and titanium dioxide (TiO₂). In some embodiments, the erodible delay member comprises hydroxypropyl cellulose (HPC), TEC, vitamin E polyethylene glycol 1000 succinate (TPGS), and TiO₂. In some embodiments, the drug component comprises the drug tofacitinib citrate, VA64, and TEC. In some embodiments, the tracking strip or tracking loop comprises barium sulfate (BaSO₄), VA64, and TEC. In some embodiments, the content of barium sulfate in the tracking strip or tracking loop is 56.5% by weight of the tracking strip or tracking loop.

In some embodiments, the oral drug dosage form of **Table 7A** comprises the weight percentages (w/w%) and total weight of the components listed in **Table 7B**.

Table 7B: Components of oral drug dosage form shown in **FIG. 13**

Component	Composition (w/w%)	Unit (mg/tablet)
Hydroxypropyl methylcellulose acetate succinate (HPMCAS)	21.74	71.82
Vitamin E polyethylene glycol 1000 succinate (TPGS)	3.06	10.10
Vinyl acetate copolymer	5.48	18.12
Triethyl citrate	16.13	53.31

Hydroxypropyl cellulose	48.78	161.20
Tofacitinib citrate	2.69	8.88
Titanium dioxide	0.18	0.58
Barium sulfate	1.94	6.40
Total weight of tablet	100	330.41

In vitro dissolution tests were performed on the oral drug dosage forms, with the *in vitro* dissolution study parameters as follows: USP device I; 0.1 N hydrochloric acid, 750 mL, 100 rpm for 2 h, then switched to pH 6.8 medium, 1000 mL, 100 rpm for several hours at 37 ± 0.5 °C, and the *in vitro* dissolution profile is shown in **FIG. 14**.

PK and X-ray studies were performed using beagle dogs. Beagle dogs (age: 15 months to 16 months; body weight: 7.9 kg to 8.8 kg) were purchased from Beijing Marshall Bioresources, Beijing, China. Each animal was individually housed in a stainless steel cage in a controlled environment (temperature 16 °C to 26 °C, humidity 40% to 70%, 12 h light/12 h dark cycle). Each dog was marked with an ear tattoo. Prior to administration, the dogs were transferred to the facility of Suzhou Chuxin Pet Hospital Co., Ltd. and acclimatized for 2 days, where animal experiments and rearing were performed.

Prior to oral administration, the dogs were deprived of food and given pentagastrin via injection to adjust the stomach to low pH, thereby simulating the pH conditions in the human stomach in fasting conditions. For animals orally receiving the oral drug dosage form, X-ray scans were recorded, and X-ray images were collected until the completion of drug release as indicated by the disappearance of barium sulfate in the oral drug dosage form. Also, blood samples were collected from the jugular veins of the beagle dogs. For animals orally receiving the reference drug Xeljanz[®] XR, only blood samples were collected from the jugular veins of the beagle dogs, and PK parameters were calculated. The X-ray images were used to assess the location, transit time, and release properties in the gastrointestinal tract at different time points. **Table 8** provides the PK results. **FIG. 15** provides the PK profiles for the oral drug dosage forms tested in the beagle dogs. **FIG. 16A** to **FIG. 16B** provide X-ray images. Each X-ray image indicated the onset of drug release and the completion of drug release.

FIG. 16A provides the X-ray images of dog with the drug described in Table 6A and

6B. The 0.5-hour X-ray image showed the drug had reached the stomach, with the tracking loop and strip intact. The 5- and 7-hour X-rays showed the drug from transverse colon to descending colon, with the completed tracking loop and strip. A 9-hour X-ray revealed a significant deformation of the tracking marker, with the tracking loop distorted and the strip bent. The deformation of the tracking markers persisted in the 10- and 11-hour X-rays, and the tracking loop became indistinguishable. A 12-hour X-ray showed the tracking loop had disappeared, leaving only the tracking strip vaguely visible.

FIG. 16B provides the X-ray images of dog with the drug described in Table 7A and 7B. The 0.5-hour X-ray image showed the drug had reached the stomach, with the tracking loop and strip intact. The 5-hour X-ray showed the drug was located in the ascending colon and the tracking marker began to deform slightly. The 6-hour X-ray revealed deformation of the tracking marker. The tracking loop was bent when viewed from the side. A 7-hour X-ray showed the tracking marker was severely deformed. The tracking loop and strip had blurred edges. No visible marks on the 8-hour X-ray image.

Table 8: PK parameters measured from beagle dogs administered oral drug dosage forms comprising tofacitinib

PK parameter		Reference (n = 6)	Table 6A and Table 6B (n = 5)	Table 7A and Table 7B (n = 5)
[#] T _{det}	h	NA	9 (8.0-11.0)	7 (6.0-8.0)
Median (range)				
[#] T _{max}	h	3 (2.0-4.0)	12 (10.0-14.0)	8 (7.0-9.0)
Median (range)				
C _{max} (mean ± SD)	ng/mL	74.4 ± 21.5	28±22.6	40.1±14.4
AUC _{0-t} (mean ± SD)	ng*h/mL	242±55.9	40.2±31.7	171±33.2
AUC _{0-inf} (mean ± SD)	ng*h/mL	252±56.3	141±69.4	184±50.0
C _{max} /dose (mean ± SD)	kg*ng/mL/mg	56.4±16.0	151±66.4	56.9±23.5
AUC _{0-t} /dose (mean ± SD)	h*kg*ng/mL/mg	183±42.5	205±107	240±52.1
AUC _{0-inf} /dose (mean ± SD)	h*kg*ng/mL/mg	191±42.4	218±102	259±81.3

Note: $^{\#}T_{det}$ and T_{max} show the median value instead of the mean and show the range instead of SD.

NA: not applicable.

The two candidate tablets and the reference drug Xeljanz[®] XR were administered to healthy subjects to verify the delivery of the colon-targeted drug *in vivo*. The study conducted X-ray imaging and pharmacokinetic studies in healthy subjects in an open-label, randomized, single dose, three phase, three sequence, and three-period crossover way. 12 healthy volunteers participated in the study. Administration in the morning under fasting conditions was performed according to a randomized schedule. There were at least 4 days of washout between each treatment. X-ray images and PK samples were acquired at predetermined time points. The intestinal transport and drug release characteristics of the tablets were evaluated by X-ray images. The plasma concentration of the drug was determined by an LC-MS/MS method. **Table 9** provides the PK results. **FIG. 17** provides the PK profiles for the oral drug dosage forms tested. **FIG. 18** provides X-ray images of humans. Each X-ray image indicates the onset of drug release and the completion of drug release.

Table 9: PK parameters (mean $\pm$ SD) for administration of oral drug dosage forms comprising tofacitinib

PK parameter		Reference (n = 12)	Table 6A and Table 6B (*n = 9)	Table 7A and Table 7B (n = 12)
T_{lag}	h	0.0 (0.0-0.0)	8.0 (7.0-11.0)	7.0 (5.0-8.0)
T_{max}	h	3.0 (2.0-5.0)	14.0 (11.0-16.0)	11.0 (9.0-14.0)
C_{max}	ng/mL	65.8 $\pm$ 22.7	17.2 $\pm$ 5.53	20.0 $\pm$ 5.80
AUC_{0-t}	ng*h/mL	525 $\pm$ 140	206 $\pm$ 69.2	231 $\pm$ 74.8
AUC_{0-inf}	ng*h/mL	530 $\pm$ 141	211 $\pm$ 70.7	234 $\pm$ 75.3

*: since the plasma concentration was below the lower limit of quantitation in 3 subjects, n = 9.

X-ray imaging results show that the candidate tablets can be traced in the gastrointestinal tract. Results from most subjects (8 out of n = 12 in both trial treatments) show that both candidate tablets released drug in the colon region: the tablet of Table 6 (3 subjects at ascending colon, 2 subjects at transverse colon, 1 subject at

transverse to descending colon, 1 subject at descending colon, 1 subject at descending to sigmoid colon), and the tablet of Table 7 (7 subjects at ascending colon, 1 subject at transverse colon).

Example 6

This example illustrates the design, manufacture, and testing of the oral drug dosage form described herein. The oral drug dosage form described herein is configured for drug release between the ileum-cecum region to the colon.

FIG. 12 provides a schematic diagram of an oral drug dosage form. To understand the erosion of the components of the oral drug dosage form, as shown in **FIGs. 19A to 19D**, various tracking strips that can be seen on an X-ray image of a patient were included. The final form of the oral drug dosage form will not comprise such a tracking strip, and such a feature part was only needed during the design stage to ensure proper targeted drug delivery. The oral drug dosage form was 3D printed using a MED 3D printing system.

As shown in **FIG. 19A**, the oral drug dosage form comprises: a drug component comprising a first erodible material admixed with a drug; and a delay component that is not admixed with the drug and comprises a pH-based enteric member and an erodible delay member. The pH-based enteric member is configured to erode at or above a predetermined pH value, and the erodible delay member comprises a second erodible material. The pH-based enteric member prevents the erosion of the erodible delay member, and the erodible delay member prevents the erosion of the drug component. After administration, the pH-based enteric member erodes, exposing the erodible delay member to the gastrointestinal fluid, such that the erodible delay member subsequently begins to erode. The erodible delay member erodes, exposing the surface of the drug component, such that the surface of the drug component erodes and the drug is released from the oral drug dosage form. As shown in **FIG. 19A**, the oral drug dosage form may comprise a tracking strip. In some embodiments, the content of barium sulfate in the tracking strip is 70.2% by weight of the tracking strip. Such a tracking strip is used to develop and optimize an oral drug dosage form. For example, after administration, imaging an individual (such as using X-rays) can be used to determine the location of

the erosion of the drug dosage form. The disclosure provided herein also encompasses oral drug dosage forms that do not have one or more tracking strips. For example, these tracking strips may not be needed after the development and optimization of an oral drug dosage form.

Table 10A and **Table 10B** provide detailed information for the oral drug dosage form shown in **FIG. 19A**.

Table 10A: Size of oral drug dosage form shown in **FIG. 19A**

Size (mm)
L1=20.5, W1=6.8, H1=5.2, H3=0.35
L2=19.7, W2=6.0, H4=0.6, H5=0.4
L3=18.1, W3=W5=4.4, H2=3.7
W4=0.4, H6=0.2

Table 10B: Components of oral drug dosage form shown in **FIG. 19A**

Component	Composition (w/w%)	Unit (mg/tablet)
Hydroxypropyl methylcellulose acetate succinate (HPMCAS)	9.07	51.82
Acetyl tri- <i>n</i> -butyl citrate (ATBC)	3.50	20
Vitamin E polyethylene glycol 1000 succinate (TPGS)	1.77	10.1
Vinyl acetate copolymer	3.17	18.12
Triethyl citrate	9.33	53.31
Hydroxypropyl cellulose	28.20	161.2
Octreotide	3.50	20
Sodium N-(8-[2-hydroxybenzoyl]-amino)caprylate (SNAC)	26.24	150
Polysorbate-80 (Tween 80)	14.00	80
Titanium dioxide	0.10	0.58
Barium sulfate	1.12	6.4

Total weight of tablet	100	571.53
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PK and X-ray studies were performed using beagle dogs. Beagle dogs (age: 15 months to 16 months; body weight: 7.9 kg to 8.8 kg) were purchased from Beijing Marshall Bioresources, Beijing, China. Each animal was individually housed in a stainless steel cage in a controlled environment (temperature 16 °C to 26 °C, humidity 40% to 70%, 12 h light/12 h dark cycle). Each dog was marked with an ear tattoo. Prior to administration, the dogs were transferred to the facility of Suzhou Chuxin Pet Hospital Co., Ltd. and acclimatized for 2 days, where animal experiments and rearing were performed. The beagle dogs were administrated orally, X-ray scans were recorded, and X-ray images were collected until the completion of drug release as indicated by the disappearance of barium sulfate in the oral drug dosage form. **FIG. 20** provides X-ray images indicating the onset of drug release.

Example 7

This example illustrates the design, manufacture, and testing of the oral drug dosage form described herein. The oral drug dosage form described herein is configured for gastric retention.

FIG. 21A and **FIG. 21B** provide schematic diagrams of an oral drug dosage form, with **FIG. 21A** providing the oral drug dosage form in a pre-administration status or a just-after-administration status and **FIG. 21B** providing the oral drug in an unfolded status. To understand the oral drug dosage form, the oral drug dosage form comprises the bottom frame 310, the cap 302, and the unfolding arm 318. The frame 310 comprises an expandable chamber therein, within which the expandable material 304 (e.g., a superabsorbent polymer) was located. One end of the unfolding arm 318 is in direct or indirect contact with the expandable material. In this example, there are also the piston 312 and the orifice 308 within the expandable chamber. When the oral drug dosage form is placed in an aqueous environment (e.g., gastric juice), the expandable material 304 absorbs water and expands, thereby pushing the piston 312 to move. The unfolding arm 318, being forced out of or farther from the cap 302, may also be configured to rotate around the cop 302 until each of the unfolding arms 316, 318, 320, and 322 reaches an extreme position away from each other. The tracking strip 311 is attached to the surface of the unfolding arm 318 of this example for tracking the location and

unfolded status of the unfolding arm, and in another embodiment, the tracking strip 311 may be located inside the unfolding arm 318.

The size and retention time of the oral drug dosage form at the time of swelling were studied *in vivo*. To achieve *in vivo* imaging, BaSO₄ was added to the compositions of the swelling material.

The bottom frame 310, the cap 302, and the unfolding arm 318 were injection molded with PLA and ABS, the swellable member was pressed from PEO:CCNa:BaSO₄ = 56:24:20, and the tracking strip 311 printed from VA64:TEC:BaSO₄ = 55:15:30.

One male beagle dog was used in this study. The beagle dog was deprived of food for 14 h while being allowed to drink water prior to administration of the oral drug dosage form. The oral drug dosage form was administered 4 h before the dog food was given, and water was given throughout the experiment. The oral drug dosage form was swallowed whole with 20 mL of water without being broken, chewed, or ground. To evaluate the retention time and status of the oral drug dosage form, X-ray images were acquired before administration and 30 min, 1.5 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 14 h, 23 h, 24 h, 30 h, 36 h, 48 h, and 52 h after administration. At each time point, front-view and side-view images were taken simultaneously. At each acquisition time point, the X-ray images, the location of the drug dosage form, and the extent to which the unfolding arm unfolded were collected, as shown in **FIG. 22A** and **FIG. 22B**. As can be seen in **FIG. 22A** and **FIG. 22B**, before the administration, the four unfolding arms were converged together, and the swellable member was in its minimum configuration. The images at 30 min and 1.5 h after administration show that the four arms unfolded from a smaller unfolding angle to a larger one, and the location of drug retention was in the stomach. The images from 3 h to 36 h after administration show that the location of drug retention was still in the stomach. The images show the four unfolding arms unfolded simultaneously with the swellable member in the maximum configuration, and the relative positions of the tracking strips on the four unfolding arms and the swellable member were not changed significantly. The images at 48 h after administration show that the drug was in the ileocecal valve, at which point the swellable member began to blur, only one of the four unfolding arms remained unfolded, and the other three were reconverged. The images at 52 h after administration show that the drug was in the colon, the swellable member had disappeared, and all four unfolding arms were converged.

According to the method, it can be determined that the oral drug dosage form has a long retention time in the stomach, the unfolding arm is in the unfolded position, and the oral drug dosage form is capable of staying in the stomach for at least about 36 h.

Example 8

This example illustrates the design, manufacture, and testing of the oral drug dosage form described herein. The oral drug dosage form described herein is configured for gastric retention.

FIG. 23A and **FIG. 23C** provide schematic diagrams of an oral drug dosage form, with **FIGs. 23A** and **23B** providing the oral drug dosage form in a pre-administration status or a just-after-administration status and **FIG. 23C** providing the oral drug in an unfolded status. The oral drug dosage form 400 comprises the body 402, the blade 404, and the blade 406. In this example, the body is located between the two blades and may be arranged in other ways. The visible marks 421, 422, and 423 are pasted or set in a 3D printing manner on the body 402 and the blades for tracking the location and the unfolded status of the unfolding arm. To understand the oral drug dosage form, the body and blades are injection molded with PLA and ABS, and the swelling material consists of PEO:CCNa = 66:34. The tracking strip is printed from EC N10:FeSO₄:DBS = 40:45:15. The body comprises the chamber 411 (not shown in the figure) and the orifice 410 connected to the chamber, and the chamber 411 comprises an expandable material. The expandable material expands to push the blades to unfold.

In order to study the size and retention time of an oral drug dosage form at the time of swelling *in vivo* and to achieve *in vivo* imaging, a tracking strip is attached to the surface of the blade for tracking the location and the unfolded status of the blade. When the drug dosage form is fully unfolded, three tracking stripes may be observed from the image data. As shown in **FIG. 23D**, **FIG. 23D** is a schematic diagram of three tracking stripes with the blades fully unfolded. The three tracking stripes are identical or similar in shape to each other, and the angle formed between the two blades at the maximum unfolding angle is 120°. When the angle of the tracking stripe of the oral drug dosage form changes, the end time of gastric retention may be determined based on the administration time of the oral drug dosage form and the eating condition. The

individual is again subjected to image tracking at the predicted end time of gastric retention to confirm the location of the drug. If the tracking strip is located in the intestinal tract, the actual gastric retention time of the drug is calculated according to the location of the drug in the intestinal tract and the transit time in the intestinal tract under the condition of large samples. If the drug is located in the stomach, the angle change of the tracking stripes is observed again, and the end time of gastric retention is determined again according to the change, the administration time of the oral drug dosage form, and the eating condition until the imaging shows that the tracking strip is located in the intestinal tract.

The gastric retention time obtained according to the above method is used to determine whether the preset time period is reached.

Example 9

This example illustrates the design, manufacture, and testing of the oral drug dosage form described herein.

FIG. 24A provides a schematic diagram of the oral drug dosage form 500. The oral drug dosage form 500 comprises the non-erodible component 502 and the drug component 504. The non-erodible component comprises a barrier material that is impermeable to bodily fluids, and the drug component comprises a first erodible material admixed with a drug. The one or more sides of the layer of the drug component are bonded to, such as in direct contact with, the non-erodible component. The oral drug dosage form 500 in **FIG. 24A** is configured such that upon administration to a human individual, the oral drug dosage form will begin to pass through the gastrointestinal system of the human individual, with the top surface of the drug component 504 exposed, allowing the release of the drug via the drug component 504 from the oral drug dosage form. To understand the erosion of the components of the oral drug dosage form, as shown in **FIG. 24A**, various tracking markers that can be seen on an X-ray image of a patient were included. The final form of the oral drug dosage form will not comprise such tracking markers, and such a feature part is only needed during the design stage to ensure proper targeted drug delivery and accurate drug release. The oral drug dosage form was 3D printed using a MED 3D printing system. As shown in **FIG.**

24A, the oral drug dosage form 500 can comprise two drug components 504. Both drug components 504 have a rounded surface and comprise a visible material to form a tracking marker. The erodible material, the drug, and the visible material forming the drug component 504 are physically premixed and then melted uniformly to prepare an intermediate or directly enter the print head to form the tracking layer.

FIG. 24B provides a schematic diagram of the oral drug dosage form 600. The oral drug dosage form 600 comprises the non-erodible component 602, the drug component 604, and the delay component 603. The non-erodible component comprises a barrier material that is impermeable to bodily fluids, the drug component comprises a first erodible material that is admixed with a drug, and the delay component comprises a second erodible material that is not admixed with the drug. The one or more sides of the layer of the drug component are bonded to, such as in direct contact with, the non-erodible component. The one or more sides of the layer of the drug component are bonded to, such as in direct contact with, the delay component. The oral drug dosage form 600 in **FIG. 24B** is configured such that upon administration to a human individual, the oral drug dosage form will begin to pass through the gastrointestinal system of the human individual, with the top surface of the delay component 603 beginning to erode; after the delay component 603 has eroded, the top surface of the drug component 604 begins to be exposed, and the drug in drug components 604 on both sides is released from the oral drug dosage form. To understand the erosion of the components of the oral drug dosage form, as shown in **FIG. 24B**, various tracking markers 605 that can be seen on an X-ray image of a patient were included. The final form of the oral drug dosage form will not comprise such tracking markers, and such a feature part is only needed during the design stage to ensure proper targeted drug delivery and accurate drug release. The oral drug dosage form was 3D printed using a MED 3D printing system. As shown in **FIG. 24B**, the oral drug dosage form 600 comprises two drug components, two delay components, and two tracking markers. The surfaces of the delay components and the drug components are all in an equilateral triangle shape, one surface of the drug component is in direct contact with a non-erodible component and the other surface of the drug component is in direct contact with an delay component, and the delay component completely covers the other surface of the drug component. The drug component 604 also comprises a visible material and is prepared in the same manner as the oral drug dosage form 500.

FIG. 24C provides a schematic diagram of the oral drug dosage form 700. The oral drug dosage form 700 comprises the non-erodible component 702, the drug component 704, and the delay component 703. The non-erodible component comprises a barrier material that is impermeable to bodily fluids, the drug component comprises a first erodible material that is admixed with a drug, and the delay component comprises a second erodible material that is not admixed with the drug. The one or more sides of the layer of the drug component are bonded to, such as in direct contact with, the non-erodible component. The one or more sides of the layer of the drug component are bonded to, such as in direct contact with, the delay component. The oral drug dosage form 700 in **FIG. 24C** is configured such that upon administration to a human individual, the oral drug dosage form will begin to pass through the gastrointestinal system of the human individual, with the top surface of the delay component 703 beginning to erode; after the delay component 703 has eroded, the top surface of the drug component begins to be exposed, and the drug in the drug component 704 is released from the oral drug dosage form. To understand the erosion of the components of the oral drug dosage form, as shown in **FIG. 24C**, various tracking markers that can be seen on an X-ray image of a patient were included. The final form of the oral drug dosage form will not comprise such tracking markers, and such a feature part is only needed during the design stage to ensure proper targeted drug delivery and accurate drug release. The oral drug dosage form was 3D printed using a MED 3D printing system. As shown in **FIG. 24C**, the oral drug dosage form 700 comprises a drug component and a delay component, both of which have rounded surfaces. One surface of the drug component is in direct contact with a non-erodible component and the other surface of the drug component is in direct contact with the delay component, and the delay component completely covers the other surface of the drug component. The drug component may comprise a tracking marker, and a visible material is homogeneously admixed with the compositions of the drug component. The drug component and the tracking marker may be prepared by MED melt extrusion to form a tracking layer.

Table 11A: Sizes of oral drug dosage forms shown in **FIG. 24A** to **FIG. 24C**

Drug dosage form 500	S1=78.56mm ² , S2=55.12 mm ² , H1=4.20mm, H2=0.42mm
Drug dosage form 600	S1=78.54 mm ² , S2=15.61 mm ² ,

	H1=4.21mm, H2=0.51mm, H3=0.96mm
Drug dosage form 700	S1=78.62 mm ² , S2=55.64mm ² , H1=4.25mm, H2=0.41mm, H3=2.89mm

Table 11B: Compositions of oral drug dosage forms shown in **FIG. 24A** to **FIG. 24C**

	Drug dosage form 500		Drug dosage form 600		Drug dosage form 700	
Component	Composition (w/w%)	Unit (mg/tablet)	Composition (w/w%)	Unit (mg/tablet)	Composition (w/w%)	Unit (mg/tablet)
Ethylcellulose	76.46	308.32	76.49	310.35	37.27	148.98
BaSO ₄	3.68	14.85	1.02	4.14	3.13	12.49
Hydroxypropyl Cellulose	/	/	3.57	14.53	38.18	152.6
Dibutyl Sebacate	16.60	66.93	16.61	67.37	8.09	32.34
PEG20000	2.45	9.92	0.97	3.94	2.90	11.58
CaHPO ₄	/	/	0.45	1.82	4.77	19.08
TiO ₂	0.19	0.75	0.19	0.76	0.09	0.36
Tofacitinib citrate	0.62	2.48	0.25	1.00	0.80	3.18
Triethyl Citrate	/	/	0.45	1.81	4.77	19.07
Total weight of tablet	100	403.25	100	405.72	100	399.68

In some embodiments, the non-erodible component consists of ethylcellulose, dibutyl sebacate, and TiO₂. In some embodiments, the drug component consists of BaSO₄, PEG20000, and tofacitinib citrate. In some embodiments, the delay component consists of hydroxypropyl cellulose, CaHPO₄, and triethyl citrate. The content of BaSO₄ in drug dosage forms 500, 600, and 700 is 54.52%, 45.63%, and 45.82%, respectively, by weight of the drug component.

The first method in General Chapter <0931>, Chinese Pharmacopoeia, Volume IV,

2020 Edition and the basket method in General Chapter <711>, United States Pharmacopeia were operated according to the regulations by using 900 mL of 0.1 mol/L hydrochloric acid as a dissolving medium at 37 °C and 100 rpm. **FIG. 25** shows the *in vitro* dissolution profiles of the drug dosage forms 500, 600, and 700. For the time points of the dissolution profile in **FIG. 25**, the data points are based on the mean of three replicates, and the standard deviation is provided using an error bar.

X-ray studies were performed using a beagle dog. The beagle dog (age: 15 months; body weight: 7.9 kg) was purchased from Beijing Marshall Bioresources, Beijing, China. The beagle dog was individually housed in a stainless steel cage in a controlled environment (temperature 16 °C to 26 °C, humidity 40% to 70%, 12 h light/12 h dark cycle). Prior to administration, the beagle dog was transferred to the facility of Suzhou Chuxin Pet Hospital Co., Ltd. and acclimatized for 2 days, where animal experiments and rearing were performed.

Prior to oral administration, the dogs were deprived of food and given pentagastrin via injection to adjust the stomach to low pH, thereby simulating the pH conditions in the human stomach in fasting conditions. The drug dosage forms 500, 600, and 700 were administered simultaneously to the beagle dog, X-ray scans were recorded, and X-ray images were collected until the completion of drug release as indicated by the disappearance of barium sulfate in the oral drug dosage forms. **FIG. 26** provides X-ray images of the three dosage forms that were clearly visible from the beginning of the administration of the drug dosage forms, illustrating that the tracking marker can be designed in any shape. After 30 min, only the drug dosage forms 600 and 700 remained in the image data, and the image of the drug dosage form 500 could not be distinguished from the image data. After 2 h, the drug dosage form 600 was shown as a discontinuous image on the image at the duodenum. After 3 h, only the drug dosage form 700 remained in the jejunum. The X-ray images obtained from the different time points indicate the onset of drug release or the completion of drug release. As can be seen in **FIG. 26**, the drug dosage form 500 completed release within 0.5 h, the drug dosage form 600 completed release within 3 h, and the drug dosage form 700 completed release within 10 h.

Example 10

This example illustrates the design, manufacture, and testing of the oral drug dosage form described herein.

The oral drug dosage form shown in FIG. 1, comprising the tracking strip shown in FIG. 2, was prepared in the same manner as in Example 1, and the size of the prepared oral drug dosage form was the same as in Example 1. Table 12 provides compositional information for the oral drug dosage form shown in FIG. 2.

Table 12: Components of oral drug dosage form shown in FIG. 2

Component	Composition (w/w%)	Unit (mg/tablet)
Poly(methacrylic acid-co-ethyl acrylate)	6.11	21.91
Vinyl acetate copolymer	24.54	88.03
Triethyl citrate	10.78	38.67
Hydroxypropyl cellulose	24.52	87.96
Anhydrous dicalcium phosphate (CaHPO4)	2.82	10.12
Tofacitinib citrate	2.36	8.47
Ethyl cellulose	22.18	79.56
Dibutyl sebacate	4.82	17.29
Titanium dioxide	0.05	0.18
Barium sulfate	1.82	6.53
Total weight of tablet	100	358.72

In some embodiments, the non-erodible component comprises ethyl cellulose (EC), dibutyl sebacate (DBS), and titanium dioxide (TiO₂). In some embodiments, the pH-based enteric member comprises vinyl acetate copolymer (VA64), poly(methacrylic acid-co-ethyl acrylate), and triethyl citrate (TEC). In some embodiments, the erodible delay member comprises hydroxypropyl cellulose, dicalcium phosphate (CaHPO₄), and TEC. In some embodiments, the drug component comprises the drug tofacitinib citrate, VA64, and TEC. In some embodiments, the tracking strip comprises barium sulfate (BaSO₄), VA64, and TEC. In some embodiments, the content of barium sulfate

in the tracking strip is 30.2% by weight of the tracking strip.

X-ray studies were performed using a beagle dog. The beagle dog (age: 15 months; body weight: 7.9 kg) was purchased from Beijing Marshall Bioresources, Beijing, China. The animal was individually housed in a stainless steel cage in a controlled environment (temperature 16 °C to 26 °C, humidity 40% to 70%, 12 h light/12 h dark cycle). Prior to administration, the dogs were transferred to the facility of Suzhou Chuxin Pet Hospital Co., Ltd. and acclimatized for 2 days, where animal experiments and rearing were performed.

Prior to oral administration, the dogs were deprived of food and given pentagastrin via injection to adjust the stomach to low pH, thereby simulating the pH conditions in the human stomach in fasting conditions. Before and after oral administration of the oral drug dosage form recorded in Table 12, X-ray scans were taken, and X-ray images were collected until the completion of drug release as indicated by the disappearance of barium sulfate in the drug component of the oral drug dosage form. The X-ray images were used to assess the location, transit time, and release properties in the gastrointestinal tract at different time points. **FIG. 27** provides X-ray images showing the status of the tracking strip clearly before and after administration of the drug dosage form as seen from the images corresponding to different times and indicating the onset and completion of drug release based on the change in the location and status of the tracking strip.

Claims

1. An oral drug dosage form comprising,
 - a drug component comprising:
 - a first erodible material admixed with a drug, and
 - a delay component comprising:
 - a second erodible material not admixed with the drug, wherein
 - the drug component is covered by or embedded in the delay component,
 - and
 - a first tracking marker comprising:
 - a third erodible material admixed with a first visible material, wherein
 - the first tracking marker has at least one face in contact with the delay component.
2. The oral drug dosage form of claim 1, wherein the first tracking marker is covered by the delay component.
3. The oral drug dosage form of any one of claims 1-2, wherein the first tracking marker and the drug component begin to erode simultaneously following contact of the oral drug dosage form to a bodily fluid in an individual.
4. The oral drug dosage form of any one of claims 1-3, wherein the oral drug dosage form further comprises a second tracking marker, which comprises a fourth erodible material admixed with a second visible material, wherein the drug component completely surrounds the second tracking marker.
5. The oral drug dosage form of claim 4, wherein the second tracking marker begins to erode after the drug component begins to erode following contact of the oral drug dosage form to a bodily fluid in an individual.
6. The oral drug dosage form of any one of claims 1-3, wherein the drug component further comprises a second tracking marker, wherein the second tracking marker comprises a second visible material admixed with the drug and the first erodible material.
7. The oral drug dosage form of any one of claims 1-6, wherein the oral drug dosage form further comprises a non-erodible component, which comprises a first non-erodible material that is not admixed with a drug.

8. The oral drug dosage form of claim 7, wherein the non-erodible component surrounds the delay component and leaves one or more openings at the top or bottom of the delay component.
9. The oral drug dosage form of any one of claims 7-8, wherein the oral drug dosage form further comprises a third tracking marker, and the non-erodible component completely surrounds the third tracking marker.
10. The oral drug dosage form of claim 9, wherein the first, second, third and fourth erodible materials may be the same or may be different.
11. The oral drug dosage form of any one of claims 9-10, wherein the first, second, third, and fourth erodible materials may be each simultaneously selected from one or more of the following materials: copovidone, polyvinylpyrrolidone-co-vinyl acetate, polyvinylpyrrolidone-polyvinyl acetate copolymer 60/40, crospovidone, polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose or hypromellose, hydroxypropyl methylcellulose phthalate, methylcellulose, methacrylic acid copolymer, poly(methacrylic acid-co-ethyl acrylate), poly(butyl methacrylate-co-(2-dimethylaminoethyl)methacrylate-co-methyl methacrylate) 1:2:1, poly(dimethylaminoethyl methacrylate-co-methacrylate), poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonium ethyl methacrylate chloride), poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1, poly(methacrylic acid-co-methyl methacrylate) 1:2, poly(methacrylic acid-co-ethyl acrylate) 1:1, poly(methacrylic acid-co-methyl methacrylate) 1:1, polyethylene oxide, polyethylene glycol, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer 57/30/13, polyethylene glycol-polyvinyl alcohol graft copolymer 25/75, Kollicoat IR-polyvinyl alcohol 60/40, polyvinyl alcohol, aminoalkyl methacrylate copolymer E, hydroxypropyl methylcellulose acetate succinate or hypromellose acetate succinate, methacrylate copolymer, ammonio alkyl methacrylate copolymer, ethylcellulose, polyvinyl acetate, polyvinylpyrrolidone 80/20, polyvinylacetal diethylamino lactate, maltitol, lactose monohydrate, xylitol, isomalt, sucrose, glucose, dextran 70, or maltose.
12. The oral drug dosage form of any one of claims 9-11, wherein the first, second, third, fourth, and fifth erodible materials may each simultaneously include a plasticizer and/or an additive.

13. The oral drug dosage form of any one of claims 1-12, wherein the delay component further comprises a pH-based enteric member configured to erode at or above a predetermined pH value.
14. The oral drug dosage form of claim 13, wherein the pH-based enteric member covers the second erodible material of the delay component.
15. The oral drug dosage form of any one of claims 13-14, wherein the first tracking marker has at least one face in contact with the second erodible material of the delay component.
16. The oral drug dosage form of any one of claims 7-15, wherein the non-erodible component comprises a barrier material that is impermeable to bodily fluids.
17. The oral drug dosage form of any one of claims 1-16, wherein the top or bottom surface of the oral drug dosage form has a shape of a circle, an ellipse, a bullet, an arrow, a triangle, an arc triangle, a square, an arc square, a rectangle, an arc rectangle, a diamond, a pentagon, a hexagon, an octagon, a half-moon, an almond, or a combination thereof.
18. The oral drug dosage form of any one of claims 7-17, wherein the non-erodible component is configured to control the exposure of the drug component and/or the delay component of the oral drug dosage form to bodily fluids.
19. The oral drug dosage form of any one of claims 1-18, wherein the first tracking marker shows a symmetrical pattern on at least one projection surface, and/or the second tracking marker shows a symmetrical pattern on at least one projection surface.
20. The oral drug dosage form of any one of claims 4-19, wherein the first tracking marker is a loop structure and the second tracking marker is a strip structure.
21. An oral drug dosage form comprising:
 - a drug component comprising:
 - a first erodible material admixed with a drug, and
 - a first tracking marker,
 - which is used for indicating whether the drug component is exposed to bodily fluids,
 - a second tracking marker,
 - which is used for indicating whether the drug component is completely

- released, and
- a cover layer comprising:
 - an erodible material, wherein
 - the cover layer surrounds the drug component, the first tracking marker, and the second tracking marker.
- 22. The oral drug dosage form of claim 21, wherein the first tracking marker and the drug component are exposed to the bodily fluids simultaneously.
- 23. The oral drug dosage form of any one of claims 21-22, wherein the second tracking marker is covered by the drug component and is in direct contact with the drug component.
- 24. The oral drug dosage form of any one of claims 21-23, wherein the shape of the surface of the second tracking marker is the same as the shape of the surface of the drug component and the second tracking marker is smaller in size than the drug component.
- 25. The oral drug dosage form of any one of claims 21-24, wherein the cover layer further comprises a non-erodible portion.
- 26. The oral drug dosage form of claim 25, wherein the second tracking marker is covered by the non-erodible portion.
- 27. The oral drug dosage form of any one of claims 21-26, wherein the first tracking marker is a loop structure.
- 28. An oral drug dosage form comprising:
 - a drug component comprising:
 - a first erodible material admixed with a drug, and
 - a delay component not admixed with the drug comprising:
 - a pH-based enteric member configured to erode at or above a pre-determined pH value; and/or
 - an erodible delay member, wherein
 - the delay component is configured to control the oral drug dosage form to start the release at a predetermined location and/or time,
 - a tracking marker comprising:
 - an indicating feature for indicating the delivery location of the drug component and/or the release of the drug, wherein

- the tracking marker is located between the drug component and the delay component.
29. The oral drug dosage form of claim 28, wherein the pH-based enteric member and/or the erodible delay member cover the tracking marker, and the tracking marker covers the drug component.
30. An oral drug dosage form comprising:
- a drug component comprising:
 - a first erodible material admixed with a drug, and
 - a tracking marker comprising:
 - an indicating feature for indicating the delivery location of the drug component and/or the release of the drug based on whether the tracking marker can be detected or deforms in an image environment.
31. The oral drug dosage form of claim 30, wherein the imaging environment includes one or more of X-ray imaging technique, magnetic resonance imaging (MRI), ultrasound imaging, computed tomography imaging (CT), or computer image recognition technique.
32. The oral drug dosage form of any one of claims 30-31, wherein the tracking marker comprises a first tracking marker that is not detectable in the imaging environment after the oral drug dosage form reaches a first predetermined location and/or a first predetermined time.
33. The oral drug dosage form of any one of claims 30-32, wherein the tracking marker further comprises a second tracking marker that deforms after the oral drug dosage form reaches a second predetermined location and/or a second predetermined time.
34. An oral drug dosage form comprising,
- a drug component comprising:
 - a first erodible material admixed with a drug, and
 - a body comprising:
 - an expandable chamber configured to contain at least a portion of an expandable material,
 - a movable component, wherein
 - at least a portion of the movable component extends out of or rotates around the body by the force provided by the expandable material;

the body and/or the movable component contains a drug thereon; and
a tracking marker, wherein
the tracking marker is loaded in the body and/or the movable component or
the tracking marker is coated on the body and/or the movable component.

35. The oral drug dosage form of claim 34, wherein the movable component comprises a groove in which the drug component is located.
36. The oral drug dosage form of claim 35, wherein the tracking marker is located in the groove and the drug component at least partially covers the tracking marker.
37. The oral drug dosage form of any one of claims 35-36, wherein the tracking marker is located at the bottom of the groove.
38. The oral drug dosage form of any one of claims 34-37, wherein the tracking marker comprises a first tracking marker that is loaded in or coated on the movable component.
39. The oral drug dosage form of claim 38, wherein the movable component is at least one movable arm, and the first tracking marker is located on the surface of the movable arm or at least partially embedded within the movable arm.
40. The oral drug dosage form of claim 39, wherein the movable component is at least three movable arms, each of which carries the first tracking marker.
41. The oral drug dosage form of any one of claims 34-40, wherein the tracking marker comprises a second tracking marker that is loaded in the body.
42. The oral drug dosage form of claim 41, wherein the second tracking marker comprises a visible material admixed with the expandable material.
43. The oral drug dosage form of claim 41, wherein the second tracking marker comprises a visible material not admixed with the expandable material.
44. The oral drug dosage form of any one of claims 34-43, wherein the expandable chamber comprises a fluid inlet for passage of a fluid, and the expandable material increases in volume upon contact with the fluid.
45. The oral drug dosage form of any one of claims 34-44, wherein the expandable material comprises sodium alginate (SA), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), hydroxypropyl methylcellulose (HPMC), polyethylene oxide (PEO), polyvinyl alcohol (PVA), microcrystalline cellulose

(MCC), croscarmellose sodium (CCNa), carboxymethylcellulose sodium (CMC-Na), polyvinylpolypyrrolidone (PVPP), sodium carboxymethyl starch (CMS-Na), polyethylene glycol (PEG), or a mixture thereof.

46. The oral drug dosage form of any one of claims 1-45, wherein the visible materials are visible under X-ray or magnetic resonance imaging (MRI), ultrasound imaging, computed tomography imaging (CT), or computer image recognition technique.
47. The oral drug dosage form of claim 46, wherein the visible materials are visible under X-ray comprises one or more of the following materials: bismuth potassium citrate, bismuth oxide, magnesium, magnesium alloy, titanium alloy, gold, platinum, barium sulfate, ferric sulfate, barium chloride, barium hydroxide, silver nitrate, tantalum chloride, barium tungstate, strontium tungstate, calcium tungstate, cobalt tungstate, cadmium tungstate, ferrous tungstate, tungsten carbide, tungsten oxide, tungsten boride, cerium oxide, meglumine diatrizoate, sodium diatrizoate, iodamide meglumine, meglumine iothalamate, iohexol, iopamidol, ioversol, metrizamide, gadofosveset trisodium, gadoxetic acid disodium, gadopentetate dimeglumine, gadobenate dimeglumine, gadodiamide, gadoversetamide, gadoteridol, manganese chloride, bismuth oxycarbonate ((BiO)₂CO₃), metal powders, and metal beads.
48. The oral drug dosage form of any one of claims 1-47, wherein the proportion of the visible material in the tracking marker is 20% or more.
49. A method of three-dimensional printing of an oral drug dosage form of any one of claims 1-48, which comprises allocating materials according to a layer-by-layer model of the oral drug dosage form to print the oral drug dosage form, wherein each layer of the layer-by-layer model is allocated the following materials as needed for printing:
 - (a) a non-erodible component material for forming any portion of the non-erodible component in the layer;
 - (b) a pH-based enteric member material for forming any portion of the pH-based enteric member in the layer;
 - (c) an erodible delay member material for forming any portion of the erodible delay member in the layer;

- (d) a drug component material for forming any portion of the drug component in the layer; and/or
 - (e) a tracking marker material for forming any portion of the tracking marker in the layer.
50. A method of three-dimensional printing of an oral drug dosage form of any one of claims 1-48, which comprises allocating materials according to a layer-by-layer model of the oral drug dosage form to print the oral drug dosage form, wherein each layer of the layer-by-layer model is allocated the following materials as needed for printing:
- (a) a pH-based enteric member material for forming any portion of the pH-based enteric member in the layer;
 - (b) an erodible delay member material for forming any portion of the erodible delay member in the layer;
 - (c) a drug component material for forming any portion of the drug component in the layer; and/or
 - (d) a tracking marker material for forming any portion of the tracking marker in the layer.
51. The method of any one of claims 49-50, wherein the allocation for the drug component, the pH-based enteric member, the erodible delay member, the non-erodible component, and/or the tracking marker is performed by different print heads, respectively.
52. A method for producing an oral drug dosage form of any one of claims 1-48, which is selected from three-dimensional printing, injection molding, ultrasonic welding, or any combination thereof, and then assembly is carried out to form the oral drug dosage form.
53. The method of claim 52, wherein the three-dimensional printing comprises allocating materials according to the layer-by-layer model of the oral drug dosage form to print the oral drug dosage form.
54. A method for verifying the release effect of an oral drug dosage form, which comprises:
- (a) administering to an individual an oral drug dosage form of any one of claims 1-

48;

- (b) imaging the individual over a time course to obtain the location and status of the tracking marker; and
 - (c) determining the release condition of the drug based on the location and the status.
55. The method of claim 54, wherein the release condition of the drug comprises whether the drug component begins to be exposed to bodily fluids.
56. The method of claim 55, wherein the release condition of the drug further comprises whether the drug has been completely released.
57. The method of any one of claims 55-56, wherein the release condition of the drug further includes the time at which the oral drug dosage form is removed from the desired location.
58. The method of claim 57, wherein the desired location includes any of the following locations: stomach, duodenum, jejunum, ileum, cecum, colon, and rectum.
59. The method of any one of claims 54-58, wherein the tracking marker comprises a first tracking marker, and whether the drug begins to be exposed to bodily fluids is determined based on whether the first tracking marker is detectable or the status of the first tracking marker.
60. The method of claim 59, wherein the status of the first tracking marker is in a pre-designed form.
61. The method of any one of claims 54-60, wherein the tracking marker comprises a second tracking marker, and whether the drug has been completely released or the time at which the drug is removed from the desired location is determined based on whether the second tracking marker is detectable or the status of the second tracking marker.
62. The method of claim 61, wherein the time at which the drug is removed from the desired location is determined based on whether the second tracking marker is detectable.
63. The method of claim 61, wherein whether the drug has been completely released is determined based on the status of the second tracking marker.
64. The method of any one of claims 61-63, wherein the status of the second tracking

marker is in a pre-designed apparent deformation or an apparent deformation of the initial status of the second tracking marker.

65. A device for testing the release effect of an oral drug dosage form, comprising
a drug component and
a tracking marker comprising:
a first tracking marker, wherein
the surface of the drug component at least partially covers the tracking marker, and
the tracking marker is used for indicating the release effect of the oral drug dosage form.
66. The device of claim 65, wherein the device further comprises a delay component that completely or partially covers the drug component.
67. The device of any one of claims 65-66, wherein the device further comprises a non-erodible component that completely or partially covers the drug component.
68. The device of any one of claims 66-67, wherein the delay component comprises an enteric member for controlling the exposure of the first tracking marker and the drug component to bodily fluids in the intestinal tract.
69. The device of any one of claims 66-67, wherein the delay component comprises an erodible delay member for controlling the exposure of the first tracking marker and the drug component to bodily fluids in the colon or ileum.
70. The device of any one of claims 65-69, wherein the tracking marker comprises a second tracking marker located inside the drug component for indicating whether the drug component has been completely released.
71. The device of any one of claims 67-70, wherein the tracking marker comprises a third tracking marker located inside the non-erodible component for indicating where the drug component is located.
72. A device for testing the erosion effect of a delay component comprised in an oral drug dosage form, comprising
a compartment formed by a first erodible material;
a delay component comprising the first erodible material, wherein
the delay component covers the compartment, and
a first tracking marker comprising:

a second erodible material admixed with a first visible material, wherein
the first tracking marker is embedded in the delay component, and
at least one face of the first tracking marker is in contact with the
compartment.

73. The device of claim 72, wherein the compartment is empty.
74. The device of claim 72, wherein the compartment is configured to contain a drug component comprising a third erodible material admixed with a drug.
75. The device of any one of claim 72 or 74, wherein the compartment comprises a second tracking marker comprising a fourth erodible material admixed with a second visible material.
76. A method for designing an oral drug dosage form configured to release a drug at a desired gastrointestinal location in an individual, which comprises:
- (a) administering to an individual an oral drug dosage form of any one of claims 1-48;
 - (b) imaging the individual over a time course to obtain the location and status of the tracking marker; and
 - (c) based on the release condition of the drug determined via the location and the status of the tracking marker, adjusting the composition and proportion of the drug component, the delay component, and/or the non-erodible component to design the oral drug dosage form configured to release the drug at the desired gastrointestinal location in the individual.
77. A method for designing an oral drug dosage form configured to release a drug at a desired gastrointestinal location in an individual, which comprises:
- (a) administering to an individual an oral drug dosage form of any one of claims 1-48;
 - (b) imaging the individual over a time course to obtain the location and status of the tracking marker; and
 - (c) based on the release condition of the drug determined via the location and the status of the tracking marker and the plasma concentration in the individual, adjusting the composition and proportion of the drug component, the delay component, and/or the non-erodible component to design the oral drug dosage form configured to release the drug at the desired gastrointestinal location in the

individual.

78. The method of claim 77, wherein one or more pharmacokinetic (PK) parameters associated with the drug are obtained after administration of the oral drug dosage form to the individual.
79. The method of claim 78, wherein the method further comprises identifying a relationship between the one or more PK parameters and the location and status information of the tracking marker.
80. The method of claim 79, wherein the method further comprises adjusting the drug component and/or the delay component or a portion thereof based on the relationship between the one or more PK parameters and the location and status information of the tracking marker.
81. A method of designing an oral drug dosage form formulated and configured to release a drug at a desired gastrointestinal location in an individual,
wherein the oral drug dosage form comprises:
 - a drug component comprising:
 - a first erodible material admixed with a drug, and
 - a first erodible tracking marker; and
 - a delay component not admixed with the drug, the delay component comprising:
 - a pH-based enteric member configured to erode at or above a pre-determined pH value; and
 - an erodible delay member comprising a second erodible material,
 - wherein the pH-based enteric member prevents erosion of the erodible delay member, and
 - wherein the erodible delay member prevents release of the drug from the drug component for at least about 30 minutes following contact of the erodible delay member to a bodily fluid in an individual,the method comprising:
 - (a) administering the oral drug dosage form to an individual;

- (b) imaging the individual over a time course to obtain a location of the oral drug dosage form and a status of the first erodible tracking marker; and
- (c) adjusting the drug component and/ or delay component, or portion thereof, based on the location and the status of the first erodible tracking marker to design the oral drug dosage form formulated and configured to release a drug at a desired gastrointestinal location in an individual.
82. The method of claim 81, wherein the first tracking marker has at least one face in contact with the erodible delay member.
83. The method of any one of claims 81-82, wherein the drug component further comprising a second erodible tracking marker which is embedded within the drug component, wherein the imaging the individual is to further obtain a status of the second erodible tracking marker.
84. The method of any one of claims 81-82, wherein the first tracking marker comprises a first developing material, which is admixed with the drug and the first erodible material.
85. The method of any one of claims 81-84, wherein the oral drug dosage form further comprises a non-erodible component, which comprises a first non-erodible material that is not admixed with a drug and a third tracking marker, wherein the imaging the individual is to further obtain a status of the third tracking marker.
86. The method of claims 85, wherein the third tracking marker has at least one face in contact with the erodible delay member.
87. The method of any one of claims 84-85, wherein the non-erodible component further comprises a fourth tracking marker which is configured to indicate the location of the non-erodible component, wherein the imaging the individual is to further obtain a status of the fourth tracking marker.
88. The method of any one of claims 81-87, wherein the adjusting is based on the location and the status of the first erodible tracking marker and/or the second erodible tracking marker and/or the third tracking marker and/or the fourth tracking marker.

89. The method of any one of claims 81-88, wherein the imaging provides a location of the oral drug dosage form when the first erodible tracking marker begins to erode.
90. The method of any one of claims 81-89, wherein the imaging provides a location of the oral drug dosage form when the first erodible tracking marker has completely eroded.
91. The method of any one of claims 81-90, wherein the adjusting comprises adjusting the delay component, or portion thereof, to increase the delay of release of the drug from the oral drug dosage form based on the location and the status of the first erodible tracking marker showing earlier than desired release.
92. The method of any one of claims 81-90, wherein the adjusting comprises adjusting the delay component, or portion thereof, to decrease the delay of release of the drug from the oral drug dosage form based on the location and the status of the first erodible tracking marker showing later than desired release.
93. The method of any one of claims 81-92, wherein the first tracking marker comprises barium sulfate.
94. The method of any one of claims 81-93, wherein the imagining comprises x-ray imaging.
95. The method of any one of claims 81-94, further comprises obtaining one or more pharmacokinetic (PK) parameters associated with the drug following the administration of the oral drug dosage form to an individual.
96. The method of any one of claims 81-95, further comprising identifying a relationship between the one or more PK parameters and the locational and status information of the first tracking marker.
97. The method of any one of claims 81-96, further comprising adjusting the drug component and/ or delay component, or portion thereof, based on the relationship between the one or more PK parameters and the locational and status information of the first tracking marker.
98. The method of any one of claims 81-97, wherein the tracking marker is selected from one or more of a tracking loop, a tracking strip, a tracking layer, or a

tracking block.

99. A method of designing an oral drug dosage form configured to release a drug at a desired gastrointestinal location in an individual,

wherein the oral drug dosage form comprises:

a drug component comprising a first erodible material admixed with a drug;

a non-erodible component; and

a delay component not admixed with the drug, the delay component comprising:

a pH-based enteric member configured to erode at or above a pre-determined pH value; and

an erodible delay member comprising a second erodible material,

wherein the pH-based enteric member prevents erosion of the erodible delay member, and

wherein the erodible delay member prevents erosion of the drug component,

wherein the oral drug dosage form comprises at least one tracking marker positioned in a component thereof,

the method comprising:

(a) administering the oral drug dosage form to an individual;

(b) imaging the individual over a time course to obtain a location of the oral drug dosage form and a status of the at least one tracking marker; and

(c) adjusting the drug component and/ or delay component and/or non-erodible component, or portion thereof, based on the location and the status of the at least one tracking marker, to design the oral drug dosage form configured to release a drug at a desired gastrointestinal location in an individual.

100. The method of claim 99, wherein a tracking marker is located in, or near, the drug component.
101. The method of claim 99 or 100, wherein a tracking marker is located in the non-erodible component.
102. The method of any one of claims 99-101, wherein a tracking marker is located in the pH-based enteric member.
103. The method of any one of claims 99-102, wherein a tracking marker is located in the erodible delay member.
104. The method of any one of claims 99-103, wherein at least one of the at least one tracking markers is erodible.
105. A method of designing an oral drug dosage form configured to release a drug at a desired gastrointestinal location in an individual, wherein the oral drug dosage form comprises:
a drug component comprising:
a first erodible material admixed with a drug, and
a body comprising:
an expandable chamber configured to contain at least a portion of an expandable material,
a movable component, wherein
at least a portion of the movable component extends out of or rotates around the body by the force provided by the expandable material; and
the body and/or the movable component contains the drug component thereon; and
a tracking marker, wherein
the oral drug dosage form comprises at least one tracking marker positioned in a component and/or the body thereof,
the method comprising:
(a) administering the oral drug dosage form to an individual;
(b) imaging the individual over a time course to obtain a location of the oral drug dosage form and a status of the at least one tracking marker; and
(c) adjusting the drug component and/ or expandable material and/or movable

component, or portion thereof, based on the location and the status of the at least one tracking marker, to design the oral drug dosage form configured to release a drug at a desired gastrointestinal location in an individual.

106. The method of claim 105, wherein a tracking marker is loaded in the body.
107. The method of any one of claims 105-106, wherein a tracking marker is loaded in the movable component.
108. The method of any one of claims 105-107, wherein a tracking marker is coated on the body.
109. The method of any one of claims 105-108, wherein a tracking marker is coated on the movable component.
110. The method of any one of claims 105-109, wherein a tracking marker is loaded in the expandable chamber.
111. The method of any one of claims 105-110, wherein the status of the tracking marker is determined based on the angle between the tracking markers.
112. The method of any one of claims 105-111, wherein the status of the tracking marker is determined based on relative position of the tracking markers.
113. The method of any one of claims 105-112, wherein the retention time of the oral drug dosage form in the stomach can be obtained based on the location and the status of the at least one tracking marker.