used to form a shape of an erodible material admixed with a drug by pouring the erodible material admixed with the drug into the negative mold (WO2017010938). The molded erodible material admixed with a drug was then manually assembled into the final drug dosage form. However, such techniques are limited, *e.g.*, limited throughput, need for extra manufacturing steps required when using a mold process, and limited drug dosage form design capability/flexibility due to the molding process.

[0005] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

SUMMARY

[0006] The present disclosure provides, *e.g.*, dosage forms configured and formulated to provide a desired release profile, and methods of designing and methods of making thereof. Although much of the application discusses drug dosage forms, such as oral drug dosage forms, one of ordinary skill in the art will readily understand that this disclosure also pertains to and teaches other dosage forms configured and formulated to provide a desired release profile of, *e.g.*, a compound, such an implant drug dosage form or a dosage form comprising a reagent (reagent dosage form) configured and formulated to provide a desired reagent release profile.

[0007] In one example, the present disclosure provides methods for three-dimensional printing of a dosage form, such as a drug dosage form (for example oral drug dosage form), formulated and configured to provide a desired release profile, such as a desired drug release profile, comprising: dispensing a first erodible material admixed with a compound (e.g., a drug) and a second material not admixed with the compound (e.g., the drug) to produce a multi-layered structure comprising a plurality of layers of the first erodible material, wherein the first erodible material is embedded in the second material, wherein each layer of the first erodible material has a pre-determined surface area, thickness, and mass fraction, such as a drug mass fraction, wherein the pre-determined surface area, thickness, and/or drug mass fraction correlate with the desired release profile, and wherein upon exposure to a bodily fluid, such as a gastrointestinal fluid, the compound (e.g., drug) is released in accordance with the desired release profile.

[0008] In some examples, the methods further comprise providing the desired release profile, such as the desired rug release profile, prior to the dispensing step.

[0009] In some examples, the methods further comprise creating a virtual image of the dosage form prior to the dispensing step.

[0010] In some examples, the methods further comprise creating a computer model that contains the pre-determined parameters prior to the dispensing step.

[0011] In some examples, the methods further comprise feeding the pre-determined parameters to the three-dimensional printer prior to the dispensing step.

[0012] In some examples, the first erodible material admixed with the compound (e.g., the drug) and the second material not admixed with the compound (e.g., the drug) are dispensed separately.

[0013] In some examples, the first erodible material admixed with the compound (e.g., the drug) and the second material not admixed with the compound (e.g., the drug) are dispensed sequentially.

[0014] In some examples, the surface areas of the first erodible material in at least two of the layers are different from each other.

[0015] In some examples, the thicknesses of each of the plurality of layers of the first erodible material are the same.

[0016] In some examples, the thickness of at least two of the layers of the first erodible materials are different from each other.

[0017] In some examples, the mass fraction, such as the drug mass fraction, in each of the plurality of layers of the first erodible material are the same.

[0018] In some examples, the mass fractions, such as drug mass fractions, in at least two of the layers of the first erodible materials are different from each other.

[0019] In some examples, the second material is a second erodible material.

[0020] In some examples, the first erodible material and the second erodible material are different from each other. In some examples, the first erodible material and the second erodible material are the same.

[0021] In some examples, the second material is an insulating material that is impermeable to the bodily fluid, such as gastrointestinal fluid, wherein the insulating material forms a barrier between the bodily fluid and at least a portion of the multi-layered structure. In some examples, the methods further comprise dispensing an insulating material that is impermeable to the bodily

fluid, such as gastrointestinal fluid, wherein the insulating material forms a barrier between the bodily fluid and at least a portion of the multi-layered structure.

[0022] In some examples, the first erodible material and the second material are dispensed by different printing heads. In some examples, the first erodible material, the second material, and the insulating material are dispensed by different printing heads.

[0023] In some examples, the three-dimensional printing is carried out by fused deposition modeling (FDM). In some examples, the FDM is a non-filament FDM. In some examples, the FDM is a filament FDM. In some examples, the three-dimensional printing is carried out by hot melt extrusion coupled with a three-dimensional printing technique, such as FDM.

[0024] In some examples, the first erodible material and the second material have the same erosion rate.

[0025] In some examples, the thickness of each layer is no more than about 0.2 mm.

[0026] In some examples, the methods further comprise dispensing an intermediate material not admixed with the drug, wherein the intermediate material forms an intermediate layer between two or more layers of the first erodible material. In some examples, the intermediate material is the same as the first erodible material or the second material.

[0027] In some examples, the methods further comprise dispensing an intermediate material not admixed with the drug, wherein the intermediate material forms an intermediate layer between two or more layers of the first erodible material. In some examples, the intermediate material is the same as the first erodible material.

[0028] In some examples, the compound (e.g., drug) is to be released at an increasing rate. In some examples, the compound (e.g., drug) is to be released at a decreasing rate. In some examples, the compound (e.g., drug) is to be released at an increasing rate followed by a decreasing rate, or vice versa. In some examples, the compound (e.g., drug) is to be released in an oscillating pattern, such as an alternating pattern.

[0029] In some examples, the dosage form, such as a drug dosage form, further comprises a, *e.g.*, second drug. In some examples, *e.g.*, the second drug is admixed with the first erodible material.

[0030] In some examples, the methods further comprise dispensing a third erodible material admixed with a, *e.g.*, second drug, wherein the multi-layered structure further comprises a plurality

of layers of the third erodible material, wherein the third material is embedded in the second material. In some examples, each layer of the third erodible material has a pre-determined surface area, thickness, and mass fraction, such as drug mass fraction, wherein the pre-determined surface area, thickness, and/or mass fraction correlate with a second desired release profile, and wherein upon exposure to the bodily fluid, such as gastrointestinal fluid, the, *e.g.*, second drug is released in accordance with the second desired release profile. In some examples, the third erodible material is the same as the first erodible material.

[0031] In some examples, the erosion of the first erodible material is pH dependent. In some examples, the erosion of the third erodible material is pH dependent.

[0032] In some examples, the drug dosage form is an oral drug dosage form. In some examples, the bodily fluid is gastrointestinal fluid.

[0033] In another example, the present disclosure provides methods of designing a dosage form, such as a drug dosage form, to provide a desired release profile, such as a desired drug release profile, wherein the dosage form comprises a multi-layered structure comprising a plurality of layers of a first erodible material admixed with a compound (e.g., a drug), wherein the first erodible material is embedded in a second material not admixed with the compound (e.g., the drug), the methods comprising: (a) selecting the first erodible material and the second material for forming the multi-layered structure; (b) obtaining an erosion rate of first erodible material; and (c) determining the thickness, surface area, and/or mass fraction, such as drug mass fraction, in each layer based on the release rate of the compound (e.g., the drug) and the desired release profile.

[0034] In some examples, the methods further comprise obtaining the desired release profile, such as the desired drug release profile.

[0035] In some examples, the methods further comprise dispensing the first erodible material admixed with the compound (e.g., the drug) and the second material not admixed with the compound (e.g., the drug) based on the determined thickness, surface area, and/or mass fraction, such as drug mass fraction.

[0036] In some examples, the methods further comprise obtaining a desired release profile, such as a desire drug release profile.

[0037] In some examples, the multi-layered structure further comprises a plurality of second layers of a third erodible material admixed with a, *e.g.*, second drug, and wherein the method further

comprises: determining the release rate of the, *e.g.*, second drug from the third erodible material; and determining the thickness, surface area, and/or mass fraction, such as drug mass fraction, in each second layer based on the release rate of the, *e.g.*, second drug and the desired release profile.

[0038] In some examples, the methods further comprise dispensing the third erodible material admixed with the, *e.g.*, second drug based on the determined thickness, surface area, and/or mass fraction, such as drug mass fraction.

[0039] In one example, the present disclosure provides methods for three-dimensional ("3D) printing of a dosage form, such as a drug dosage form, formulated and configured to provide a desired release profile, such as a desired drug release profile, wherein the dosage form comprises a multi-layered structure comprising a plurality of layers of a first erodible material admixed with a compound (e.g., a drug), wherein the first erodible material is embedded in a second material not admixed with the compound (e.g., the drug), the method comprising: (a) determining the thickness, surface area, and/or mass fraction, such as drug mass fraction, in each layer based on the release rate of the compound (e.g., the drug) and the desired release profile; and (b) dispensing the first erodible material admixed with the compound (e.g., the drug) and the second material not admixed with the compound (e.g., the drug) based on the determined thickness, surface area, and/or mass fraction, such as drug mass fraction.

[0040] In some examples, the thickness (H) of the layer of the first erodible material is determined based on the erosion rate of the first erodible material admixed with the drug (v_E) and the time interval between two different datapoints on the drug release profile (t_E), wherein

$$H = t_E * v_E.$$

[0041] In some examples, the mass fraction (m_F), such as drug mass fraction, in the first erodible material is determined based on the percentage, in decimal form, of the total compound (e.g., drug) in the dosage form that is in the layer of the erodible material admixed with the compound (e.g., drug) (%L), the total mass of the compound (e.g., the drug) in the drug dosage form (m_{DTot}), the density of the erodible material admixed with the compound (e.g., the drug) (ρ), and the volume (V_{vol}) of the layer of the erodible material, wherein

$$m_F = \frac{\%_L * m_{DTot}}{\rho * V_{vol}}.$$

[0042] In some examples, the total surface area (S_t) of the layers of the first erodible material that are exposed to the bodily fluid, such as gastrointestinal fluid, at the same time is determined by the mass fraction (m_F), such as drug mass fraction, and the thickness of the layers of first erodible material, wherein

$$S_t = \frac{\%_L * m_{DTot}}{\rho * H * m_F}.$$

[0043] In some examples, the methods further comprise: (i) determining the release profile, such as the drug release profile, of the produced dosage form; (ii) comparing the release profile of the dosage form with the desired release profile; and (iii) adjusting the design of the dosage form by altering one or more of: the first erodible material, the second material, the surface area of the one or more of the layers of the first erodible material, the thickness of one or more layers of the first erodible material, and the mass fraction of the compound (e.g., the drug) in one or more layers of the first erodible material.

[0044] In some examples, there is provided a method for three-dimensional ("3D") printing of an oral drug dosage form formulated and configured to provide a desired drug release profile, wherein the drug dosage form comprises a multi-layered structure comprising a plurality of layers of a first erodible material admixed with a drug having a pre-determined drug mass faction (m_F), wherein the first erodible material is embedded in a second material not admixed with the drug, the method comprising: (a) dividing the desired drug release profile into a plurality of time intervals (t_n), each time interval corresponding to a layer in the multi-layered structure; (b) calculating the percentage of drugs to be released during each time interval ($\%_L$); (c) calculating the thickness of each layer (H_n) of the multi-layered structure based on the erosion rate of the first erodible material(V), wherein $H_n=t_n*V$; (d) calculating the surface area of each layer based on $\%_L$, H_n, m_F, total amount of drug in the oral drug dosage form (m_{DTot}), and the density of the first erodible material (ρ), wherein:

$$S_n = \frac{\%_L * m_{DTot}}{\rho * Hn * m_F}$$

(e) dispensing the first erodible material admixed with the drug based on the determined H_n and S_n for each layer, thereby printing the multi-layered structure; and (f) before, after, or during step (e), dispensing the second material not admixed with the drug. In one aspect, the present disclosure refers to a method for three-dimensional printing of an oral drug dosage form formulated and configured to provide a desired drug release profile, wherein the drug dosage form comprises a multi-layered structure comprising a plurality of layers of a first erodible material admixed with a drug having a pre-determined drug mass fraction (m_F), wherein the first erodible material is embedded in a second material not admixed with the drug, the method comprising: (a) dividing the desired drug release profile into a plurality of time intervals (t_n), each time interval corresponding to a layer in the multi-layered structure; (b) calculating the percentage of drugs to be released during each time interval ($\%_L$); (c) calculating the thickness of each layer (H_n) of the multi-layered structure based on the erosion rate of the first erodible material(V), wherein $H_n=t_n*V$; (d) calculating the surface area of each layer based on $\%_L$, H_n, m_F, total amount of drug in the oral drug dosage form (m_{DTot}), and the density of the first erodible material (ρ), wherein:

$$S_n = \frac{\%_L * m_{DTot}}{\rho * Hn * m_F};$$

(e) dispensing the first erodible material admixed with the drug based on the determined H_n and S_n for each layer, thereby printing the multi-layered structure; (f) before, after, or during step (e), dispensing the second material not admixed with the drug.

[0045] In some examples, the 3D printing method further comprises dispensing a top erodible material not admixed with the drug on top of the multi-layered structure to form a top layer, wherein the surface area of the top layer is the same or larger than the first layer of the multi-layered structure immediately underneath the top layer. In some examples, the thickness of the top layer is determined based on the delay time needed for the drug release from the multi-layered structure. In some examples, the top erodible material is the same as the first erodible material. In some examples, the top erodible material is different from the first erodible material.

[0046] In some examples according any one of the 3D printing methods described above, the second material is erodible, and can have the same or a different erosion rate as that of the first erodible material. In other examples, the second material is an insulating material that is impermeable to bodily fluid, wherein the insulating material forms a barrier between the bodily fluid and at least a portion of the multi-layered structure.

[0047] In some examples according to any one of the 3D printing methods described above, further comprising dispensing an insulating material that is impermeable to bodily fluid, wherein the insulating material forms a barrier between the bodily fluid and at least a portion of the multi-layered structure.

[0048] In some examples according to any one of the 3D printing methods described above, further comprising dispensing an intermediate material not admixed with the drug, wherein the intermediate material forms one or more intermediate layers between two or more layers of the first erodible material. In some examples, the intermediate material is the same as the first erodible material. In some examples, the intermediate layer is different from the first erodible material.

[0049] In some examples according to any of the 3D printing methods described above, wherein the three-dimensional printing is carried out by fused deposition modeling (FDM), such as non-filament FDM. In some examples, the first erodible material and the second material are printed by different printing heads. In some examples, the first erodible material and the top erodible material are printed by different printing heads. In some examples, the first erodible material, the second erodible material (if any), and the insulating material are printed by a different printing heads.

[0050] The method of any one of the 3D printing methods described above, further comprising: i) determining the drug release profile of the oral drug dosage form produced by the method of any

one of the 3D printing methods described above; ii) comparing the drug release profile of the oral drug dosage form with the desired drug release profile; iii) adjusting one or more parameters selected from: the first erodible material, the second material, the surface area of the one or more of the layers of the first erodible material, the thickness of one or more layers of the first erodible material, and the mass fraction of the drug in one or more layers of the first erodible material; and iv) three-dimensional printing of a second oral drug dosage form based on the adjusted parameters.

[0051] In some examples according any one of the 3D printing method described above, wherein the release profile of the oral drug dosage form or second drug oral dosage form is equivalent to the desired release profile based on Chow's method or similarity factor calculation method.

[0052] In some examples according to any one of the 3D printing method described above, the method further comprises creating a virtual image of the drug dosage form prior to the dispending steps, creating a computer model that contains the pre-determined parameters prior to the dispensing step, and/or feeding the pre-determined parameters to the three-dimensional printer prior to the dispensing step.

[0053] In some examples according to any one of the 3D printing method described above, the surface area of each of the plurality of the layers of the first erodible material in the multi-layered structure decreases sequentially from the surface to the interior of the oral dosage form, wherein when the oral dosage form is exposed to a bodily fluid the plurality of layers are exposed to the bodily fluid in a sequential pattern, with the layer with the largest surface area exposed to the bodily fluid first.

[0054] In some examples according to any one of the 3D printing method described above, the oral drug dosage form comprises two or more multi-layered structures.

[0055] In some examples, there is provided a method for three-dimensional ("3D") printing of an oral drug dosage form formulated and configured to provide a first desired drug release profile and a second desired drug release profile, wherein the drug dosage form comprises a first multi-layered structure comprising a plurality of layers of a first erodible material admixed with a drug having a pre-determined drug mass faction (m_F), wherein the first erodible material is embedded in a second material not admixed with a first drug, and a second multi-layered structure comprising a plurality of layers of a third erodible material admixed with a second drug having a pre-determined

drug mass faction, wherein the third erodible material is embedded in a fourth material not admixed with the drug, the method comprising: (a) dividing each of the desired drug release profile into a plurality of time intervals (t_n), each time interval corresponding to a layer in a corresponding multi-layered structure; (b) calculating the percentage of drugs to be released during each time interval ($\%_L$); (c) calculating the thickness of each layer (H_n) of the multi-layered structures based on the erosion rate of the first erodible material or third erodible material (V), wherein $H_n=t_n*V$; (d) calculating the surface area of each layer based on $\%_L$, H_n, m_F, total amount of drug in the oral drug dosage form (m_{DTot}), and the density of the first or first erodible material (ρ), wherein:

$$S_n = \frac{\%_L * m_{DTot}}{\rho * Hn * m_F}$$

(e) dispensing the first erodible material admixed with the first drug and third erodible material admixed with the second drug based on the determined H_n and S_n for each layer, thereby printing the two multi-layered structures; and (f) before, after, or during step (e), dispensing the second material and fourth material not admixed with the drug. In one aspect, the present disclosure refers to a method for three-dimensional printing of an oral drug dosage form formulated and configured to provide a first desired drug release profile and a second desired drug release profile, wherein the drug dosage form comprises a first multi-layered structure comprising a plurality of layers of a first erodible material admixed with a drug having a pre-determined drug mass fraction (m_F), wherein the first erodible material is embedded in a second material not admixed with a first drug, and a second multi-layered structure comprising a plurality of layers of a third erodible material admixed with a second drug having a pre-determined drug mass fraction, wherein the third erodible material is embedded in a fourth material not admixed with the drug, the method comprising: (a) dividing each of the desired drug release profile into a plurality of time intervals (t_n), each time interval corresponding to a layer in a corresponding multi-layered structure; (b) calculating the percentage of drugs to be released during each time interval ($\%_L$); (c) calculating the thickness of each layer (H_n) of the multi-layered structures based on the erosion rate of the first erodible material or third erodible material (V), wherein $H_n=t_n*V$; (d) calculating the surface area of each layer based on $\%_L$, H_n, m_F, total amount of drug in the oral drug dosage form (m_{DTot}), and the density of the first or third erodible material (ρ), wherein:

$$S_n = \frac{\%_L * m_{DTot}}{\rho * Hn * m_F};$$

(e) dispensing the first erodible material admixed with the first drug and third erodible material admixed with the second drug based on the determined H_n and S_n for each layer, thereby printing the two multi-layered structures; (f) before, after, or during step (e), dispensing the second material and fourth material not admixed with the drug. In some examples, the first erodible material and the third erodible material are the same. In some examples, the second and fourth materials are the same. In some examples, the first drug and the second drug are the same. In some examples, the first drug and the second drug are different.

[0056] In another example, the present disclosure provides dosage forms, such as oral dosage forms, produced according to any one of the methods described herein. In one aspect, the present disclosure refers to an oral dosage form produced by the method as disclosed herein. In some examples, the dosage form, such as drug dosage form, further comprises an enteric coating.

[0057] These and other examples and advantages of the present disclosure will become apparent from the subsequent detailed description and the appended claims. It is to be understood that one, some, or all of the properties of the various examples described herein may be combined to form other examples of the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0058] **FIG. 1** shows an exemplary schematic **100** for designing a drug dosage form **160** formulated and configured to provide a desired drug release profile **105**.

[0059] **FIGS. 2A-2C** show exemplary drug dosage forms **200**, **240**, **265** formulated and configured to provide a desired drug release profile. **FIG. 2A** shows a cross-sectional view of the