

SOLID ORAL DOSAGE FORMS, KITS, AND METHODS OF USING THE SAME**BACKGROUND**

[0001] The Centers for Disease Control (CDC) estimates that 20-30% of new prescriptions are never filled at the pharmacy and medications are not taken as prescribed 50% of the time. Patient nonadherence causes 30-50% of chronic disease treatment failures.^[1] The number of pills per dose and the number of doses per day are key factors that contribute to patient nonadherence.^[2] Short elimination half-time of drugs causes a high pill burden, especially from long-term medication.

SUMMARY OF THE INVENTION

[0002] Provided herein are solid oral dosage forms, methods, and kits useful, *e.g.*, for the extension of the residence time of active pharmaceutical agents *in vivo* by the synthesis of a polymer *in situ* in a subject. In one aspect, provided herein is a solid oral dosage form comprising a first layer and a second layer wherein: the first layer comprises a monomer and an oxygen source; the second layer comprises an active pharmaceutical agent; and the monomer further comprises a backbone molecule.

[0003] In another aspect, this disclosure provides a method of administering an active pharmaceutical ingredient to a subject in need thereof, the method comprising administering to the subject the solid oral dosage form described herein.

[0004] In a further aspect, provided herein a method of reducing the dosing frequency of an active pharmaceutical ingredient in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form of the present disclosure.

[0005] In another aspect, provided herein a method of prolonging gastrointestinal retention of an active pharmaceutical ingredient in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form described herein.

[0006] In one aspect, provided herein a method of sustaining the release of an active pharmaceutical ingredient in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form of the present disclosure.

[0007] In one aspect, this disclosure provides a method of treating a bacterial infection in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form of the present disclosure.

[0008] In another aspect, provided herein a method of treating infectious disease in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form disclosed herein.

[0009] In one aspect of the present disclosure, is provided a method of treating a symptom of Parkinson's disease in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form described herein.

[0010] In another aspect, provided herein a method of increasing the half-life of an active pharmaceutical agent in the subject, the method comprising administering to the subject the solid oral dosage form of the present disclosure.

[0011] In a further aspect, this disclosure provides a method of increasing residence time of an active pharmaceutical agent in the subject, the method comprising administering to the subject the solid oral dosage form disclosed herein.

[0012] In another aspect, provided herein a kit comprising: a solid oral dosage form disclosed herein, and instructions for administering the solid oral dosage form to a subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] The accompanying drawings, which constitute a part of this specification, illustrate several embodiments of the invention and together with the description, provide non-limiting examples of the invention. The figures are exemplary and do not limit the scope of the present disclosure.

[0014] **FIGs. 1A-C** show a schematic illustrating a triple-layer pill and the gelation and adhesion process of Alginate-dopamine on the small intestine facilitated by catalase enzyme.

Fig. 1A shows an illustration of a size tunable triple layer pill, and a mucoadhesive layer comprising Alginate-dopamine, tris, dopamine, and hydrogen peroxide. Also shown is a diagram illustrating small-intestine specific adhesion. **Fig. 1B** shows a schematic of the Alginate-dopamine gelation. **Fig. 1C** shows the tissue interfacial crosslinking and self-crosslinking of the polydopamine polymer.

[0015] **FIG. 2A** shows an exemplary synthesis process of an alginate-dopamine monomer.

FIG. 2B shows ^1H NMR spectra of alginate, dopamine and an alginate-dopamine monomer.

FIG. 2C shows UV-Vis spectra of an alginate-dopamine monomer. **FIG. 2D** shows FTIR

spectra of alginate, dopamine, and an alginate-dopamine monomer. **FIG. 2E** shows rheological properties of an alginate-dopamine hydrogel. The storage (G') and loss (G'') moduli of the 2 % (w/v) alginate-dopamine hydrogel and 4% (w/v) alginate-dopamine

hydrogel at a frequency sweep mode are provided. **FIG. 2F** shows before and after photos of ALG-DA gelation. **FIG. 2G** shows SEM images of alginate-dopamine hydrogel at 2% weight by volume and 4% weight by volume. Scale bar, 100 μ m.

[0016] **FIG. 3A** shows an illustration of the oxidation reaction of alginate-dopamine (ALG-DA) pill on different parts of gastrointestinal (GI) tract. **FIG. 3B** shows a schematic of ALG-DA adhesive hydrogel formation on tissue. **FIG. 3C** shows photographs of ALG-DA pills gelation on different parts of GI tract of pigs *in vitro* at different time-points. **FIG. 3D** shows the gelation degree calculation of ALG-DA pills on different parts of GI tract of pigs *in vitro*. Data are represented as mean $\pm$ S.D., $n = 3$, *indicates $p < 0.05$. **FIG. 3E** shows endoscopic views of ALG-DA pills gelation *in vivo* after 10 minutes of attachment to small intestine of pigs *in vivo*.

[0017] **FIGs. 4A-4E** show adhesion and erosion assessment of alginate-dopamine pills. **FIG. 4A** shows a schematic representation of an instrument used to conduct a washing setup. **FIG. 4B** shows photographs of alginate-dopamine pills (ALG-DA) and alginate-calcium pills (ALG-Ca) adhesion performance after water flushing within 10 seconds. **FIG. 4C** shows retention time of ALG-DA pills and ALG-Ca pills on small intestine after water flushing, $n=30$. **FIG. 4D** shows photographs of the erosion of ALG-DA pills and alginate (ALG) pills on small intestine over time. Graphite was added in the ALG pills in order to investigate the erosion process (dark color). **FIG. 4E** shows change in pill size for ALG-DA pills and ALG pills after water flushing for 30 minutes. Data are represented as mean $\pm$ S.D., $n = 4$.

[0018] **FIGs. 5A-5B** show drug delivery evaluation *in vitro* and *in vivo*. **FIG. 5A** shows mean *in vitro* drug release of amoxicillin and levodopa/carbidopa in the middle layer of triple-layer pills ($n = 3$). **FIG. 5B** shows GI tract residence of control pills and alginate-dopamine (ALG-DA) pills via X-ray imaging. Data are represented as mean $\pm$ S.D., $n = 3$.

[0019] **FIGs. 6A-6D** show drug delivery pharmacokinetic evaluation *in vivo*. **FIG. 6A** shows the serum concentration-time curve of amoxicillin when administered as control pills and ALG-DA pills in pigs. Data are represented as mean $\pm$ S.D., $n = 3$. **FIG. 6B** shows the pharmacokinetic parameters of amoxicillin when administered as control pills and ALG-DA pills in pigs. Data are represented as mean $\pm$ S.D., $n = 3$. **FIG. 6C** shows the serum concentration-time curve of levodopa when administered as control pills and ALG-DA pills in pigs. Data are represented as mean $\pm$ S.D., $n = 3$. **FIG. 6D** shows the pharmacokinetic parameters of levodopa when administered as control pills and ALG-DA pills in pigs. Data are represented as mean $\pm$ S.D., $n = 3$. *indicates $p < 0.05$, which demonstrates that differences

are statistically significant. N.S. indicates that differences are not statistically significant, independent sample T-test.

[0020] **FIG. 7** shows swelling of hydrogels. A swelling assay was performed to assess the cross-linking of 1 % (w/v), 2% (w/v), 4% (w/v) alginate-dopamine hydrogels. Data are reported as means $\pm$ S.D., $n = 3$.

[0021] **FIGs. 8A-8B** show a size of polymerization of dopamine. **FIG. 8A** shows graphs of polymerization of dopamine (PDA) via dynamic light scattering (DLS). **FIG. 8B** shows sizes of PDA for different concentration (0.5 %, 1 %, 2 % w/v) via DLS. Data are reported as means $\pm$ S.D., $n = 3$.

[0022] **FIGs. 9A-9B** show drug release *in vitro* from pills of different formulations. **FIG. 9A** shows amoxicillin release from pills composed of 10% HPMC (low viscosity), 20% HPMC (low viscosity) and 50% HPMC (high viscosity). **FIG. 9B** shows levodopa and carbidopa release from pills composed of 10% HPMC (low viscosity) and 20% HPMC (low viscosity). Data are represented as mean $\pm$ S.D., $n = 3$.

[0023] **FIGs. 10A-10B** show the biocompatibility of alginate-dopamine hydrogel to various cell lines. **FIG. 10A** shows the results of an MTT assay of the proliferation of cells cultured with alginate-dopamine hydrogel for 6 hours ($n = 4$). **FIG. 10B** shows the results of an MTT assay of the proliferation of cells cultured with alginate-dopamine hydrogel for 24 hours ($n = 4$). Dotted lines indicate 80% and 90% survival rate.

[0024] **FIG. 11** shows the weight of rats. Rats of control group were orally gavaged with water ($n = 5$) daily for 1 month, and rats of drug group were orally gavaged with pill formulation ingredients (60 mg per kg rat, $n = 5$) daily for 28 days.

[0025] **FIGs. 12A-12J** show representative histology images of rat tissues and pig small intestine. For the control group (left), SD rats were orally gavaged with the same volume of water ($n = 5$) daily for 28 days, and for the Test group (right), SD rats were orally gavaged with ALG-DA pill ingredients (60 mg per kg rat, $n = 5$) daily for 28 days. Scale bar, 100 μ m or 200 μ m. **FIG. 12A** shows representative histology images of rat brain. **FIG. 12B** shows representative histology images of rat heart. **FIG. 12C** shows representative histology images of rat liver. **FIG. 12D** shows representative histology images of rat spleen. **FIG. 12E** shows representative histology images of rat lung. **FIG. 12F** shows representative histology images of rat kidney. **FIG. 12G** shows representative histology images of rat stomach. **FIG. 12H** shows representative histology images of rat small intestine. **FIG. 12I** shows representative

histology images of rat colon. **FIG. 12J** shows representative histology images of pig small intestine. Pills were put on the small intestine for 6 hours via laparotomy. Scale bar, 1mm.

[0026] **FIG. 13** is a table showing biochemical indexes of rat blood after rats were gavaged with water (n = 5) and pill formulation ingredients daily for 28 days.

[0027] **FIG. 14** is a table showing complete blood counts data. Rats were gavaged with water (Control, n = 5) and pill ingredients (Test, n=5) daily for 28 days.

[0028] **FIG. 15** shows a schematic of an exemplary triple layer tablet and sustained release of the active pharmaceutical ingredient (API) according to the present disclosure.

DEFINITIONS

[0029] Unless otherwise required by context, singular terms shall include pluralities, and plural terms shall include the singular.

[0030] The language “in some embodiments” and “in certain embodiments” are used interchangeably.

[0031] The following definitions are more general terms used throughout the present application:

[0032] The singular terms “a,” “an,” and “the” include plural references unless the context clearly indicates otherwise. Similarly, the word “or” is intended to include “and” unless the context clearly indicates otherwise.

[0033] Other than in the examples, or where otherwise indicated, all numbers expressing quantities of ingredients or reaction conditions used herein should be understood as modified in all instances by the term “about.” “About” and “approximately” shall generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Exemplary degrees of error are within 20 percent (%), typically, within 10%, or more typically, within 5%, 4%, 3%, 2%, or 1% of a given value or range of values.

[0034] When a range of values (“range”) is listed, it is intended to encompass each value and sub-range within the range. A range is inclusive of the values at the two ends of the range unless otherwise provided.

[0035] The terms “composition” and “formulation” are used interchangeably.

[0036] The terms “condition,” “disease,” and “disorder” are used interchangeably.

[0037] A “subject” to which administration is contemplated refers to a human (*i.e.*, male or female of any age group, *e.g.*, pediatric subject (*e.g.*, infant, child, or adolescent) or adult subject (*e.g.*, young adult, middle-aged adult, or senior adult)) or non-human animal. In

certain embodiments, the non-human animal is a mammal (*e.g.*, primate (*e.g.*, cynomolgus monkey or rhesus monkey), commercially relevant mammal (*e.g.*, cattle, pig, horse, sheep, goat, cat, or dog), or bird (*e.g.*, commercially relevant bird, such as chicken, duck, goose, or turkey)). In certain embodiments, the non-human animal is a fish, reptile, or amphibian. The non-human animal may be a male or female at any stage of development. The non-human animal may be a transgenic animal or genetically engineered animal. The term “patient” refers to a human subject in need of treatment of a disease.

[0038] The term “administer,” “administering,” or “administration” refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing a solid oral dosage described herein in or on a subject.

[0039] The terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease described herein. In some embodiments, treatment may be administered after one or more signs or symptoms of the disease have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease. For example, treatment may be administered to a susceptible subject prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of exposure to a pathogen). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[0040] An “effective amount” of a solid oral dosage form described herein refers to an amount sufficient to elicit the desired biological response. An effective amount of a solid oral dosage form described herein may vary depending on such factors as the desired biological endpoint, severity of side effects, disease, or disorder, the identity, pharmacokinetics, and pharmacodynamics of the particular solid oral dosage form, the condition being treated, the mode, route, and desired or required frequency of administration, the species, age and health or general condition of the subject. In certain embodiments, an effective amount is a therapeutically effective amount. In certain embodiments, an effective amount is a prophylactic treatment. In certain embodiments, an effective amount is the amount of a solid oral dosage form is described herein in a single dose. In certain embodiments, an effective amount is the combined amounts of a solid oral dosage form described herein in multiple doses. In certain embodiments, the desired dosage is delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage is delivered using

multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[0041] A “proliferative disease” refers to a disease that occurs due to abnormal growth or extension by the multiplication of cells (Walker, *Cambridge Dictionary of Biology*; Cambridge University Press: Cambridge, UK, 1990). A proliferative disease may be associated with: 1) the pathological proliferation of normally quiescent cells; 2) the pathological migration of cells from their normal location (*e.g.*, metastasis of neoplastic cells); 3) the pathological expression of proteolytic enzymes such as the matrix metalloproteinases (*e.g.*, collagenases, gelatinases, and elastases); or 4) the pathological angiogenesis as in proliferative retinopathy and tumor metastasis. Exemplary proliferative diseases include cancers (*i.e.*, “malignant neoplasms”), benign neoplasms, angiogenesis, inflammatory diseases, and autoimmune diseases.

[0042] The term “angiogenesis” refers to the physiological process through which new blood vessels form from pre-existing vessels. Angiogenesis is distinct from vasculogenesis, which is the *de novo* formation of endothelial cells from mesoderm cell precursors. The first vessels in a developing embryo form through vasculogenesis, after which angiogenesis is responsible for most blood vessel growth during normal or abnormal development. Angiogenesis is a vital process in growth and development, as well as in wound healing and in the formation of granulation tissue. However, angiogenesis is also a fundamental step in the transition of tumors from a benign state to a malignant one, leading to the use of angiogenesis inhibitors in the treatment of cancer. Angiogenesis may be chemically stimulated by angiogenic proteins, such as growth factors (*e.g.*, VEGF). “Pathological angiogenesis” refers to abnormal (*e.g.*, excessive or insufficient) angiogenesis that amounts to and/or is associated with a disease.

[0043] The terms “neoplasm” and “tumor” are used herein interchangeably and refer to an abnormal mass of tissue wherein the growth of the mass surpasses and is not coordinated with the growth of a normal tissue. A neoplasm or tumor may be “benign” or “malignant,” depending on the following characteristics: degree of cellular differentiation (including morphology and functionality), rate of growth, local invasion, and metastasis. A “benign neoplasm” is generally well differentiated, has characteristically slower growth than a malignant neoplasm, and remains localized to the site of origin. In addition, a benign neoplasm does not have the capacity to infiltrate, invade, or metastasize to distant sites. Exemplary benign neoplasms include, but are not limited to, lipoma, chondroma, adenomas, acrochordon, senile angiomas, seborrheic keratoses, lentigos, and sebaceous hyperplasias. In

some cases, certain “benign” tumors may later give rise to malignant neoplasms, which may result from additional genetic changes in a subpopulation of the tumor’s neoplastic cells, and these tumors are referred to as “pre-malignant neoplasms.” An exemplary pre-malignant neoplasm is a teratoma. In contrast, a “malignant neoplasm” is generally poorly differentiated (anaplasia) and has characteristically rapid growth accompanied by progressive infiltration, invasion, and destruction of the surrounding tissue. Furthermore, a malignant neoplasm generally has the capacity to metastasize to distant sites. The term “metastasis,” “metastatic,” or “metastasize” refers to the spread or migration of cancerous cells from a primary or original tumor to another organ or tissue and is typically identifiable by the presence of a “secondary tumor” or “secondary cell mass” of the tissue type of the primary or original tumor and not of that of the organ or tissue in which the secondary (metastatic) tumor is located. For example, a prostate cancer that has migrated to bone is said to be metastasized prostate cancer and includes cancerous prostate cancer cells growing in bone tissue.

[0044] The term “cancer” refers to a class of diseases characterized by the development of abnormal cells that proliferate uncontrollably and have the ability to infiltrate and destroy normal body tissues. *See e.g., Stedman’s Medical Dictionary*, 25th ed.; Hensyl ed.; Williams & Wilkins: Philadelphia, 1990. Exemplary cancers include, but are not limited to, acoustic neuroma; adenocarcinoma; adrenal gland cancer; anal cancer; angiosarcoma (*e.g.*, lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma); appendix cancer; benign monoclonal gammopathy; biliary cancer (*e.g.*, cholangiocarcinoma); bladder cancer; breast cancer (*e.g.*, adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast); brain cancer (*e.g.*, meningioma, glioblastomas, glioma (*e.g.*, astrocytoma, oligodendroglioma), medulloblastoma); bronchus cancer; carcinoid tumor; cervical cancer (*e.g.*, cervical adenocarcinoma); choriocarcinoma; chordoma; craniopharyngioma; colorectal cancer (*e.g.*, colon cancer, rectal cancer, colorectal adenocarcinoma); connective tissue cancer; epithelial carcinoma; ependymoma; endotheliosarcoma (*e.g.*, Kaposi’s sarcoma, multiple idiopathic hemorrhagic sarcoma); endometrial cancer (*e.g.*, uterine cancer, uterine sarcoma); esophageal cancer (*e.g.*, adenocarcinoma of the esophagus, Barrett’s adenocarcinoma); Ewing’s sarcoma; ocular cancer (*e.g.*, intraocular melanoma, retinoblastoma); familial hypereosinophilia; gall bladder cancer; gastric cancer (*e.g.*, stomach adenocarcinoma); gastrointestinal stromal tumor (GIST); germ cell cancer; head and neck cancer (*e.g.*, head and neck squamous cell carcinoma, oral cancer (*e.g.*, oral squamous cell carcinoma), throat cancer (*e.g.*, laryngeal cancer, pharyngeal

cancer, nasopharyngeal cancer, oropharyngeal cancer)); hematopoietic cancers (*e.g.*, leukemia such as acute lymphocytic leukemia (ALL) (*e.g.*, B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (*e.g.*, B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (*e.g.*, B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (*e.g.*, B-cell CLL, T-cell CLL)); lymphoma such as Hodgkin lymphoma (HL) (*e.g.*, B-cell HL, T-cell HL) and non-Hodgkin lymphoma (NHL) (*e.g.*, B-cell NHL such as diffuse large cell lymphoma (DLCL) (*e.g.*, diffuse large B-cell lymphoma), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (*e.g.*, mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (*i.e.*, Waldenström's macroglobulinemia), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (*e.g.*, cutaneous T-cell lymphoma (CTCL) (*e.g.*, mycosis fungoides, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM)), heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease); hemangioblastoma; hypopharynx cancer; inflammatory myofibroblastic tumors; immunocytic amyloidosis; kidney cancer (*e.g.*, nephroblastoma *a.k.a.* Wilms' tumor, renal cell carcinoma); liver cancer (*e.g.*, hepatocellular cancer (HCC), malignant hepatoma); lung cancer (*e.g.*, bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung); leiomyosarcoma (LMS); mastocytosis (*e.g.*, systemic mastocytosis); muscle cancer; myelodysplastic syndrome (MDS); mesothelioma; myeloproliferative disorder (MPD) (*e.g.*, polycythemia vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) *a.k.a.* myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)); neuroblastoma; neurofibroma (*e.g.*, neurofibromatosis (NF) type 1 or type 2, schwannomatosis); neuroendocrine cancer (*e.g.*, gastroenteropancreatic neuroendocrine tumor (GEP-NET), carcinoid tumor); osteosarcoma (*e.g.*, bone cancer); ovarian cancer (*e.g.*, cystadenocarcinoma, ovarian embryonal carcinoma, ovarian

adenocarcinoma); papillary adenocarcinoma; pancreatic cancer (*e.g.*, pancreatic adenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors); penile cancer (*e.g.*, Paget's disease of the penis and scrotum); pinealoma; primitive neuroectodermal tumor (PNT); plasma cell neoplasia; paraneoplastic syndromes; intraepithelial neoplasms; prostate cancer (*e.g.*, prostate adenocarcinoma); rectal cancer; rhabdomyosarcoma; salivary gland cancer; skin cancer (*e.g.*, squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)); small bowel cancer (*e.g.*, appendix cancer); soft tissue sarcoma (*e.g.*, malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma); sebaceous gland carcinoma; small intestine cancer; sweat gland carcinoma; synovium; testicular cancer (*e.g.*, seminoma, testicular embryonal carcinoma); thyroid cancer (*e.g.*, papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer); urethral cancer; vaginal cancer; and vulvar cancer (*e.g.*, Paget's disease of the vulva).

[0045] Exemplary biotherapeutic anti-cancer agents include, but are not limited to, interferons, cytokines (*e.g.*, tumor necrosis factor, interferon α , interferon γ), vaccines, hematopoietic growth factors, monoclonal serotherapy, immunostimulants and/or immunomodulatory agents (*e.g.*, IL-1, 2, 4, 6, or 12), immune cell growth factors (*e.g.*, GM-CSF) and antibodies (*e.g.* HERCEPTIN (trastuzumab), T-DM1, AVASTIN (bevacizumab), ERBITUX (cetuximab), VECTIBIX (panitumumab), RITUXAN (rituximab), BEXXAR (tositumomab)). Exemplary chemotherapeutic agents include, but are not limited to, anti-estrogens (*e.g.* tamoxifen, raloxifene, and megestrol), LHRH agonists (*e.g.* goserelin and leuprolide), anti-androgens (*e.g.* flutamide and bicalutamide), photodynamic therapies (*e.g.* vertoporphin (BPD-MA), phthalocyanine, photosensitizer Pc4, and demethoxy-hypocrellin A (2BA-2-DMHA)), nitrogen mustards (*e.g.* cyclophosphamide, ifosfamide, trofosfamide, chlorambucil, estramustine, and melphalan), nitrosoureas (*e.g.* carmustine (BCNU) and lomustine (CCNU)), alkylsulphonates (*e.g.* busulfan and treosulfan), triazenes (*e.g.* dacarbazine, temozolomide), platinum containing compounds (*e.g.* cisplatin, carboplatin, oxaliplatin), vinca alkaloids (*e.g.* vincristine, vinblastine, vindesine, and vinorelbine), taxoids (*e.g.* paclitaxel or a paclitaxel equivalent such as nanoparticle albumin-bound paclitaxel (ABRAXANE), docosahexaenoic acid bound-paclitaxel (DHA-paclitaxel, Taxoprexin), polyglutamate bound-paclitaxel (PG-paclitaxel, paclitaxel poliglumex, CT-2103, XYOTAX), the tumor-activated prodrug (TAP) ANG1005 (Angiopep-2 bound to three molecules of paclitaxel), paclitaxel-EC-1 (paclitaxel bound to the erbB2-recognizing peptide EC-1), and

glucose-conjugated paclitaxel, *e.g.*, 2'-paclitaxel methyl 2-glucopyranosyl succinate; docetaxel, taxol), epipodophyllins (*e.g.* etoposide, etoposide phosphate, teniposide, topotecan, 9-aminocamptothecin, camptoirinotecan, irinotecan, crisnatol, mytomyacin C), anti-metabolites, DHFR inhibitors (*e.g.* methotrexate, dichloromethotrexate, trimetrexate, edatrexate), IMP dehydrogenase inhibitors (*e.g.* mycophenolic acid, tiazofurin, ribavirin, and EICAR), ribonucleotide reductase inhibitors (*e.g.* hydroxyurea and deferoxamine), uracil analogs (*e.g.* 5-fluorouracil (5-FU), floxuridine, doxifluridine, ratitrexed, tegafur-uracil, capecitabine), cytosine analogs (*e.g.* cytarabine (ara C), cytosine arabinoside, and fludarabine), purine analogs (*e.g.* mercaptopurine and Thioguanine), Vitamin D3 analogs (*e.g.* EB 1089, CB 1093, and KH 1060), isoprenylation inhibitors (*e.g.* lovastatin), dopaminergic neurotoxins (*e.g.* 1-methyl-4-phenylpyridinium ion), cell cycle inhibitors (*e.g.* staurosporine), actinomycin (*e.g.* actinomycin D, dactinomycin), bleomycin (*e.g.* bleomycin A2, bleomycin B2, peplomycin), anthracycline (*e.g.* daunorubicin, doxorubicin, pegylated liposomal doxorubicin, idarubicin, epirubicin, pirarubicin, zorubicin, mitoxantrone), MDR inhibitors (*e.g.* verapamil), Ca²⁺ ATPase inhibitors (*e.g.* thapsigargin), imatinib, thalidomide, lenalidomide, tyrosine kinase inhibitors (*e.g.*, axitinib (AG013736), bosutinib (SKI-606), cediranib (RECENTINTM, AZD2171), dasatinib (SPRYCEL®, BMS-354825), erlotinib (TARCEVA®), gefitinib (IRESSA®), imatinib (Gleevec®, CGP57148B, STI-571), lapatinib (TYKERB®, TYVERB®), lestaurtinib (CEP-701), neratinib (HKI-272), nilotinib (TASIGNA®), semaxanib (semaxinib, SU5416), sunitinib (SUTENT®, SU11248), toceranib (PALLADIA®), vandetanib (ZACTIMA®, ZD6474), vatalanib (PTK787, PTK/ZK), trastuzumab (HERCEPTIN®), bevacizumab (AVASTIN®), rituximab (RITUXAN®), cetuximab (ERBITUX®), panitumumab (VECTIBIX®), ranibizumab (Lucentis®), nilotinib (TASIGNA®), sorafenib (NEXAVAR®), everolimus (AFINITOR®), alemtuzumab (CAMPATH®), gemtuzumab ozogamicin (MYLOTARG®), temsirolimus (TORISEL®), ENMD-2076, PCI-32765, AC220, dovitinib lactate (TKI258, CHIR-258), BIBW 2992 (TOVOKTM), SGX523, PF-04217903, PF-02341066, PF-299804, BMS-777607, ABT-869, MP470, BIBF 1120 (VARGATEF®), AP24534, JNJ-26483327, MGCD265, DCC-2036, BMS-690154, CEP-11981, tivozanib (AV-951), OSI-930, MM-121, XL-184, XL-647, and/or XL228), proteasome inhibitors (*e.g.*, bortezomib (VELCADE)), mTOR inhibitors (*e.g.*, rapamycin, temsirolimus (CCI-779), everolimus (RAD-001), ridaforolimus, AP23573 (Ariad), AZD8055 (AstraZeneca), BEZ235 (Novartis), BGT226 (Novartis), XL765 (Sanofi Aventis), PF-4691502 (Pfizer), GDC0980 (Genetech), SF1126 (Semafoe) and OSI-027

(OSI)), oblimersen, gemcitabine, carminomycin, leucovorin, pemetrexed, cyclophosphamide, dacarbazine, procarbazine, prednisolone, dexamethasone, campathecin, plicamycin, asparaginase, aminopterin, methopterin, porfiromycin, melphalan, leurosidine, leurosine, chlorambucil, trabectedin, procarbazine, discodermolide, carminomycin, aminopterin, and hexamethyl melamine.

[0046] The term “toxic” refers to a substance showing detrimental, deleterious, harmful, or otherwise negative effects on a subject, tissue, or cell when or after administering the substance to the subject or contacting the tissue or cell with the substance, compared to the subject, tissue, or cell prior to administering the substance to the subject or contacting the tissue or cell with the substance. In certain embodiments, the effect is death or destruction of the subject, tissue, or cell. In certain embodiments, the effect is a detrimental effect on the metabolism of the subject, tissue, or cell. The term “nontoxic” refers to a substance that is not toxic.

[0047] Anti-cancer agents encompass biotherapeutic anti-cancer agents as well as chemotherapeutic agents.

[0048] Exemplary chemotherapeutic agents include, but are not limited to, anti-estrogens (*e.g.*, tamoxifen, raloxifene, and megestrol), LHRH agonists (*e.g.*, goserelin and leuprolide), anti-androgens (*e.g.*, flutamide and bicalutamide), photodynamic therapies (*e.g.*, vertoporphin (BPD-MA), phthalocyanine, photosensitizer Pc4, and demethoxy-hypocrellin A (2BA-2-DMHA)), nitrogen mustards (*e.g.*, cyclophosphamide, ifosfamide, trofosfamide, chlorambucil, estramustine, and melphalan), nitrosoureas (*e.g.*, carmustine (BCNU) and lomustine (CCNU)), alkylsulphonates (*e.g.*, busulfan and treosulfan), triazenes (*e.g.*, dacarbazine, temozolomide), platinum containing compounds (*e.g.*, cisplatin, carboplatin, oxaliplatin), vinca alkaloids (*e.g.*, vincristine, vinblastine, vindesine, and vinorelbine), taxoids (*e.g.*, paclitaxel or a paclitaxel equivalent such as nanoparticle albumin-bound paclitaxel (ABRAXANE), docosahexaenoic acid bound-paclitaxel (DHA-paclitaxel, Taxoprexin), polyglutamate bound-paclitaxel (PG-paclitaxel, paclitaxel poliglumex, CT-2103, XYOTAX), the tumor-activated prodrug (TAP) ANG1005 (Angiopep-2 bound to three molecules of paclitaxel), paclitaxel-EC-1 (paclitaxel bound to the erbB2-recognizing peptide EC-1), and glucose-conjugated paclitaxel, *e.g.*, '2'-paclitaxel methyl 2-glucopyranosyl succinate; docetaxel, taxol), epipodophyllins (*e.g.*, etoposide, etoposide phosphate, teniposide, topotecan, 9-aminocamptothecin, camptothecin, irinotecan, crisnatol, mytomyin C), anti-metabolites, DHFR inhibitors (*e.g.*, methotrexate, dichloromethotrexate, trimetrexate,

edatrexate), IMP dehydrogenase inhibitors (*e.g.*, mycophenolic acid, tiazofurin, ribavirin, and EICAR), ribonucleotide reductase inhibitors (*e.g.*, hydroxyurea and deferoxamine), uracil analogs (*e.g.*, 5-fluorouracil (5-FU), floxuridine, doxifluridine, ratitrexed, tegafur-uracil, capecitabine), cytosine analogs (*e.g.*, cytarabine (ara C), cytosine arabinoside, and fludarabine), purine analogs (*e.g.*, mercaptopurine and Thioguanine), Vitamin D3 analogs (*e.g.*, EB 1089, CB 1093, and KH 1060), isoprenylation inhibitors (*e.g.*, lovastatin), dopaminergic neurotoxins (*e.g.*, 1-methyl-4-phenylpyridinium ion), cell cycle inhibitors (*e.g.*, staurosporine), actinomycin (*e.g.*, actinomycin D, dactinomycin), bleomycin (*e.g.*, bleomycin A2, bleomycin B2, peplomycin), anthracycline (*e.g.*, daunorubicin, doxorubicin, pegylated liposomal doxorubicin, idarubicin, epirubicin, pirarubicin, zorubicin, mitoxantrone), MDR inhibitors (*e.g.*, verapamil), Ca^{2+} ATPase inhibitors (*e.g.*, thapsigargin), imatinib, thalidomide, lenalidomide, tyrosine kinase inhibitors (*e.g.*, axitinib (AG013736), bosutinib (SKI-606), cediranib (RECENTINTM, AZD2171), dasatinib (SPRYCEL[®], BMS-354825), erlotinib (TARCEVA[®]), gefitinib (IRESSA[®]), imatinib (Gleevec[®], CGP57148B, STI-571), lapatinib (TYKERB[®], TYVERB[®]), lestaurtinib (CEP-701), neratinib (HKI-272), nilotinib (TASIGNA[®]), semaxanib (semaxinib, SU5416), sunitinib (SUTENT[®], SU11248), toceranib (PALLADIA[®]), vandetanib (ZACTIMA[®], ZD6474), vatalanib (PTK787, PTK/ZK), trastuzumab (HERCEPTIN[®]), bevacizumab (AVASTIN[®]), rituximab (RITUXAN[®]), cetuximab (ERBITUX[®]), panitumumab (VECTIBIX[®]), ranibizumab (Lucentis[®]), nilotinib (TASIGNA[®]), sorafenib (NEXAVAR[®]), everolimus (AFINITOR[®]), alemtuzumab (CAMPATH[®]), gemtuzumab ozogamicin (MYLOTARG[®]), temsirolimus (TORISEL[®]), ENMD-2076, PCI-32765, AC220, dovitinib lactate (TKI258, CHIR-258), BIBW 2992 (TOVOKTM), SGX523, PF-04217903, PF-02341066, PF-299804, BMS-777607, ABT-869, MP470, BIBF 1120 (VARGATEF[®]), AP24534, JNJ-26483327, MGCD265, DCC-2036, BMS-690154, CEP-11981, tivozanib (AV-951), OSI-930, MM-121, XL-184, XL-647, and/or XL228), proteasome inhibitors (*e.g.*, bortezomib (VELCADE)), mTOR inhibitors (*e.g.*, rapamycin, temsirolimus (CCI-779), everolimus (RAD-001), ridaforolimus, AP23573 (Ariad), AZD8055 (AstraZeneca), BEZ235 (Novartis), BGT226 (Novartis), XL765 (Sanofi Aventis), PF-4691502 (Pfizer), GDC0980 (Genetech), SF1126 (Semafoe) and OSI-027 (OSI)), oblimersen, gemcitabine, carminomycin, leucovorin, pemetrexed, cyclophosphamide, dacarbazine, procarbazine, prednisolone, dexamethasone, campathecin, plicamycin, asparaginase, aminopterin, methopterin, porfiromycin, melphalan, leurosine, leurosine,

chlorambucil, trabectedin, procarbazine, discodermolide, carminomycin, aminopterin, and hexamethyl melamine.

[0049] The terms “inflammatory disease” and “inflammatory condition” are used interchangeably herein, and refer to a disease or condition caused by, resulting from, or resulting in inflammation. Inflammatory diseases and conditions include those diseases, disorders or conditions that are characterized by signs of pain (dolor, from the generation of noxious substances and the stimulation of nerves), heat (calor, from vasodilatation), redness (rubor, from vasodilatation and increased blood flow), swelling (tumor, from excessive inflow or restricted outflow of fluid), and/or loss of function (functio laesa, which can be partial or complete, temporary or permanent. Inflammation takes on many forms and includes, but is not limited to, acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing, seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative inflammation. The term “inflammatory disease” may also refer to a dysregulated inflammatory reaction that causes an exaggerated response by macrophages, granulocytes, and/or T-lymphocytes leading to abnormal tissue damage and/or cell death. An inflammatory disease can be either an acute or chronic inflammatory condition and can result from infections or non-infectious causes. Inflammatory diseases include, without limitation, atherosclerosis, arteriosclerosis, autoimmune disorders, multiple sclerosis, systemic lupus erythematosus, polymyalgia rheumatica (PMR), gouty arthritis, degenerative arthritis, tendonitis, bursitis, psoriasis, cystic fibrosis, arthroseitis, rheumatoid arthritis, inflammatory arthritis, Sjogren’s syndrome, giant cell arteritis, progressive systemic sclerosis (scleroderma), ankylosing spondylitis, polymyositis, dermatomyositis, pemphigus, pemphigoid, diabetes (*e.g.*, Type I), myasthenia gravis, Hashimoto’s thyroiditis, Graves’ disease, Goodpasture’s disease, mixed connective tissue disease, sclerosing cholangitis, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, pernicious anemia, inflammatory dermatoses, usual interstitial pneumonitis (UIP), asbestosis, silicosis, bronchiectasis, berylliosis, talcosis, pneumoconiosis, sarcoidosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, giant cell interstitial pneumonia, cellular interstitial pneumonia, extrinsic allergic alveolitis, Wegener’s granulomatosis and related forms of angiitis (temporal arteritis and polyarteritis nodosa), inflammatory dermatoses, hepatitis, delayed-type hypersensitivity reactions (*e.g.*, poison ivy

dermatitis), pneumonia, respiratory tract inflammation, Adult Respiratory Distress Syndrome (ARDS), encephalitis, immediate hypersensitivity reactions, asthma, hay fever, allergies, acute anaphylaxis, rheumatic fever, glomerulonephritis, pyelonephritis, cellulitis, cystitis, chronic cholecystitis, ischemia (ischemic injury), reperfusion injury, allograft rejection, host-versus-graft rejection, appendicitis, arteritis, blepharitis, bronchiolitis, bronchitis, cervicitis, cholangitis, chorioamnionitis, conjunctivitis, dacryoadenitis, dermatomyositis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, gingivitis, ileitis, iritis, laryngitis, myelitis, myocarditis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, pharyngitis, pleuritis, phlebitis, pneumonitis, proctitis, prostatitis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, testitis, tonsillitis, urethritis, urocystitis, uveitis, vaginitis, vasculitis, vulvitis, vulvovaginitis, angitis, chronic bronchitis, osteomyelitis, optic neuritis, temporal arteritis, transverse myelitis, necrotizing fasciitis, and necrotizing enterocolitis. An ocular inflammatory disease includes, but is not limited to, post-surgical inflammation.

[0050] Additional exemplary inflammatory conditions include, but are not limited to, inflammation associated with acne, anemia (*e.g.*, aplastic anemia, hemolytic autoimmune anemia), asthma, arteritis (*e.g.*, polyarteritis, temporal arteritis, periarteritis nodosa, Takayasu's arteritis), arthritis (*e.g.*, crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis and Reiter's arthritis), ankylosing spondylitis, amylosis, amyotrophic lateral sclerosis, autoimmune diseases, allergies or allergic reactions, atherosclerosis, bronchitis, bursitis, chronic prostatitis, conjunctivitis, Chagas disease, chronic obstructive pulmonary disease, dermatomyositis, diverticulitis, diabetes (*e.g.*, type I diabetes mellitus, Type II diabetes mellitus), a skin condition (*e.g.*, psoriasis, eczema, burns, dermatitis, pruritus (itch)), endometriosis, Guillain-Barre syndrome, infection, ischemic heart disease, Kawasaki disease, glomerulonephritis, gingivitis, hypersensitivity, headaches (*e.g.*, migraine headaches, tension headaches), ileus (*e.g.*, postoperative ileus and ileus during sepsis), idiopathic thrombocytopenic purpura, interstitial cystitis (painful bladder syndrome), gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.*, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischemic colitis, diversion colitis, Behcet's

syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), lupus, multiple sclerosis, morphea, myasthenia gravis, myocardial ischemia, nephrotic syndrome, pemphigus vulgaris, pernicious anemia, peptic ulcers, polymyositis, primary biliary cirrhosis, neuroinflammation associated with brain disorders (*e.g.*, Parkinson's disease, Huntington's disease, and Alzheimer's disease), prostatitis, chronic inflammation associated with cranial radiation injury, pelvic inflammatory disease, reperfusion injury, regional enteritis, rheumatic fever, systemic lupus erythematosus, scleroderma, sarcoidosis, spondyloarthropathies, Sjogren's syndrome, thyroiditis, transplantation rejection, tendonitis, trauma or injury (*e.g.*, frostbite, chemical irritants, toxins, scarring, burns, physical injury), vasculitis, vitiligo and Wegener's granulomatosis. In certain embodiments, the inflammatory disorder is selected from arthritis (*e.g.*, rheumatoid arthritis), inflammatory bowel disease, inflammatory bowel syndrome, asthma, psoriasis, endometriosis, interstitial cystitis and prostatitis. In certain embodiments, the inflammatory condition is an acute inflammatory condition (*e.g.*, for example, inflammation resulting from infection). In certain embodiments, the inflammatory condition is a chronic inflammatory condition (*e.g.*, conditions resulting from asthma, arthritis and inflammatory bowel disease). The solid oral dosage forms disclosed herein may also be useful in treating inflammation associated with trauma and non-inflammatory myalgia. The solid oral dosage forms disclosed herein may also be useful in treating inflammation associated with cancer

[0051] An "autoimmune disease" refers to a disease arising from an inappropriate immune response of the body of a subject against substances and tissues normally present in the body. In other words, the immune system mistakes some part of the body as a pathogen and attacks its own cells. This may be restricted to certain organs (*e.g.*, in autoimmune thyroiditis) or involve a particular tissue in different places (*e.g.*, Goodpasture's disease which may affect the basement membrane in both the lung and kidney). The treatment of autoimmune diseases is typically with immunosuppression, *e.g.*, medications which decrease the immune response. Exemplary autoimmune diseases include, but are not limited to, glomerulonephritis, Goodpasture's syndrome, necrotizing vasculitis, lymphadenitis, peri-arteritis nodosa, systemic lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, , psoriasis, ulcerative colitis, systemic sclerosis, dermatomyositis/polymyositis, anti-phospholipid antibody syndrome, scleroderma, pemphigus vulgaris, ANCA-associated vasculitis (*e.g.*, Wegener's granulomatosis, microscopic polyangiitis), uveitis, Sjogren's syndrome, Crohn's disease,

Reiter's syndrome, ankylosing spondylitis, Lyme disease, Guillain-Barré syndrome, Hashimoto's thyroiditis, and cardiomyopathy.

[0052] A "painful condition" or "pain disorder" includes, but is not limited to, neuropathic pain (*e.g.*, peripheral neuropathic pain), central pain, deafferentation pain, chronic pain (*e.g.*, chronic nociceptive pain, and other forms of chronic pain such as post-operative pain, *e.g.*, pain arising after hip, knee, or other replacement surgery), pre-operative pain, stimulus of nociceptive receptors (nociceptive pain), acute pain (*e.g.*, phantom and transient acute pain), noninflammatory pain, inflammatory pain, pain associated with cancer, wound pain, burn pain, postoperative pain, pain associated with medical procedures, pain resulting from pruritus, painful bladder syndrome, pain associated with premenstrual dysphoric disorder and/or premenstrual syndrome, pain associated with chronic fatigue syndrome, pain associated with pre-term labor, pain associated with withdrawal symptoms from drug addiction, joint pain, arthritic pain (*e.g.*, pain associated with crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis or Reiter's arthritis), lumbosacral pain, musculo-skeletal pain, headache, migraine, muscle ache, lower back pain, neck pain, toothache, dental/maxillofacial pain, visceral pain and the like. One or more of the painful conditions contemplated herein can comprise mixtures of various types of pain provided above and herein (*e.g.* nociceptive pain, inflammatory pain, neuropathic pain, *etc.*). In some embodiments, a particular pain can dominate. In other embodiments, the painful condition comprises two or more types of pains without one dominating. A skilled clinician can determine the dosage to achieve a therapeutically effective amount for a particular subject based on the painful condition.

[0053] Infectious diseases, as described herein, are selected from viral, bacterial, protozoological, prion and other infectious diseases. Non-limiting examples of infectious diseases include: Acinetobacter infections, African sleeping sickness (African trypanosomiasis), AIDS (Acquired immunodeficiency syndrome), Amoebiasis, Anaplasmosis, Anthrax, Appendicitis, Arcanobacterium haemolyticum infections, Argentine hemorrhagic fever, Ascariasis, Aspergillosis, Astrovirus infections, Athlete's foot, Babesiosis, Bacillus cereus infections, Bacterial meningitis, Bacterial pneumonia, Bacterial vaginosis (BV), Bacteroides infections, Balantidiasis, Baylisascaris infections, Bilharziosis, BK virus infections, Black piedra, Blastocystis hominis infections, Blastomycosis, Bolivian hemorrhagic fever, Borrelia infections (Borreliosis), Botulism (and Infant botulism), Bovine tapeworm, Brazilian hemorrhagic fever, Brucellosis, Burkholderia infections, Buruli ulcer,

Calicivirus infections (Norovirus and Sapovirus), Campylobacteriosis, Candidiasis (Candidosis), Canine tapeworm infections, Cat-scratch disease, Chagas Disease (American trypanosomiasis), Chancroid, Chickenpox, Chlamydia infections, Chlamydia trachomatis infections, Chlamydophila pneumoniae infections, Cholera, Chromoblastomycosis, Climatic bubo, Clonorchiasis, Clostridium difficile infections, Coccidioidomycosis, Cold, Colorado tick fever (CTF), Common cold (Acute viral rhinopharyngitis; Acute coryza), Condyloma acuminata, Conjunctivitis, Creutzfeldt-Jakob disease (CJD), Crimean-Congo hemorrhagic fever (CCHF), Cryptococcosis, Cryptosporidiosis, Cutaneous larva migrans (CLM), Cutaneous Leishmaniasis, Cyclosporiasis, Cysticercosis, Cytomegalovirus infections, Dengue fever, Dermatophytosis, Dientamoebiasis, Diphtheria, Diphyllbothriasis, Donavanosis, Dracunculiasis, Early summer meningoencephalitis (FSME), Ebola hemorrhagic fever, Echinococcosis, Ehrlichiosis, Enterobiasis (Pinworm infections), Enterococcus infections, Enterovirus infections, Epidemic typhus, Epiglottitis, Epstein-Barr Virus Infectious Mononucleosis, Erythema infectiosum (Fifth disease), Exanthem subitum, Fasciolopsiasis, Fasciolosis, Fatal familial insomnia (FFI), Fifth disease, Filariasis, Fish poisoning (Ciguatera), Fish tapeworm, Flu, Food poisoning by Clostridium perfringens, Fox tapeworm, Free-living amebic infections, Fusobacterium infections, Gas gangrene, Geotrichosis, Gerstmann-Strüssler-Scheinker syndrome (GSS), Giardiasis, Glanders, Gnathostomiasis, Gonorrhea, Granuloma inguinale (Donovanosis), Group A streptococcal infections, Group B streptococcal infections, Haemophilus influenzae infections, Hand foot and mouth disease (HFMD), Hantavirus Pulmonary Syndrome (HPS), Helicobacter pylori infections, Hemolytic-uremic syndrome (HUS), Hemorrhagic fever with renal syndrome (HFRS), Henipavirus infections, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E, Herpes simplex, Herpes simplex type I, Herpes simplex type II, Herpes zoster, Histoplasmosis, Hollow warts, Hookworm infections, Human bocavirus infections, Human ewingii ehrlichiosis, Human granulocytic anaplasmosis (HGA), Human metapneumovirus infections, Human monocytic ehrlichiosis, Human papillomavirus (HPV) infections, Human parainfluenza virus infections, Hymenolepiasis, Influenza, Isosporiasis, Japanese encephalitis, Kawasaki disease, Keratitis, Kingella kingae infections, Kuru, Lambliasis (Giardiasis), Lassa fever, Legionellosis (Legionnaires' disease, Pontiac fever), Leishmaniasis, Leprosy, Leptospirosis, Lice, Listeriosis, Lyme borreliosis, Lyme disease, Lymphatic filariasis (Elephantiasis), Lymphocytic choriomeningitis, Malaria, Marburg hemorrhagic fever (MHF), Marburg virus, Measles, Melioidosis (Whitmore's disease), Meningitis,

Meningococcal disease, Metagonimiasis, Microsporidiosis, Miniature tapeworm, Miscarriage (prostate inflammation), Molluscum contagiosum (MC), Mononucleosis, Mumps, Murine typhus (Endemic typhus), Mycetoma, Mycoplasma hominis, Mycoplasma pneumonia, Myiasis, Nappy/diaper dermatitis, Neonatal conjunctivitis (Ophthalmia neonatorum), Neonatal sepsis (Chorioamnionitis), Nocardiosis, Noma, Norwalk virus infections, Onchocerciasis (River blindness), Osteomyelitis, Otitis media, Paracoccidioidomycosis (South American blastomycosis), Paragonimiasis, Paratyphus, Pasteurellosis, Pediculosis capitis (Head lice), Pediculosis corporis (Body lice), Pediculosis pubis (Pubic lice, Crab lice), Pelvic inflammatory disease (PID), Pertussis (Whooping cough), Pfeiffer's glandular fever, Plague, Pneumococcal infections, Pneumocystis pneumonia (PCP), Pneumonia, Polio (childhood lameness), Poliomyelitis, Porcine tapeworm, Prevotella infections, Primary amoebic meningoencephalitis (PAM), Progressive multifocal leukoencephalopathy, Pseudocroup, Psittacosis, Q fever, Rabbit fever, Rabies, Rat-bite fever, Reiter's syndrome, Respiratory syncytial virus infections (RSV), Rhinosporidiosis, Rhinovirus infections, Rickettsial infections, Rickettsialpox, Rift Valley fever (RVF), Rocky mountain spotted fever (RMSF), Rotavirus infections, Rubella, Salmonella paratyphus, Salmonella typhus, Salmonellosis, SARS (Severe Acute Respiratory Syndrome), Scabies, Scarlet fever, Schistosomiasis (Bilharziosis), Scrub typhus, Sepsis, Shigellosis (Bacillary dysentery), Shingles, Smallpox (Variola), Soft chancre, Sporotrichosis, Staphylococcal food poisoning, Staphylococcal infections, Strongyloidiasis, Syphilis, Taeniasis, Tetanus, Three-day fever, Tick-borne encephalitis, Tinea barbae (Barber's itch), Tinea capitis (Ringworm of the Scalp), Tinea corporis (Ringworm of the Body), Tinea cruris (Jock itch), Tinea manuum (Ringworm of the Hand), Tinea nigra, Tinea pedis (Athlete's foot), Tinea unguium (Onychomycosis), Tinea versicolor (Pityriasis versicolor), Toxocariasis (Ocular Larva Migrans (OLM) and Visceral Larva Migrans (VLM)), Toxoplasmosis, Trichinellosis, Trichomoniasis, Trichuriasis (Whipworm infections), Tripper, Trypanosomiasis (sleeping sickness), Tsutsugamushi disease, Tuberculosis, Tularemia, Typhus, Typhus fever, Ureaplasma urealyticum infections, Vaginitis (Colpitis), Variant Creutzfeldt-Jakob disease (vCJD, nvCJD), Venezuelan equine encephalitis, Venezuelan hemorrhagic fever, Viral pneumonia, Visceral Leishmaniasis, Warts, West Nile Fever, Western equine encephalitis, White piedra (Tinea blanca), Whooping cough, Yeast fungus spots, Yellow fever, Yersinia pseudotuberculosis infections, Yersiniosis, and Zygomycosis. In some embodiments, the present disclosure provides methods for treating an infectious disease, comprising administering to a subject suffering

therefrom an effective amount of a provided solid oral dosage form. In some embodiments, a provided method comprises administering an effective amount of a provided solid oral dosage form and another therapeutic agent known for treatment of an infectious disease.

[0054] In some embodiments, a provided method for treating an infectious disease includes administering to a patient in need thereof a provided solid oral dosage form and another therapeutic agent that is an anti-infectious disease agent. Exemplary anti-infectious disease agents are widely known in the art, including but not limited to β -Lactam Antibiotics such as Penicillin G, Amoxicillin, Penicillin V, Cloxacillin, Dicloxacillin, Methicillin, Nafcillin, Oxacillin, Ampicillin, moxycillin, Bacampicillin, Azlocillin, Carbenicillin, Mezlocillin, Piperacillin and Ticarcillin; Aminoglycosides: Amikacin, Gentamicin, Kanamycin, Neomycin, Netilmicin, Streptomycin and Tobramycin; Macrolides such as Azithromycin, Clarithromycin, Erythromycin, Lincomycin and Clindamycin Troleandomycin; Tetracyclines such as Demeclocycline, Doxycycline, Minocycline, Oxytetracycline and Tetracycline; Quinolones such as Cinoxacin and Nalidixic Acid; Fluoroquinolones such as Ciprofloxacin, Enoxacin, Grepafloxacin, Levofloxacin, Lomefloxacin, Norfloxacin, Ofloxacin, Sparfloxacin and Trovafloxacin; Polypeptides such as Bacitracin, aminocyclitol (*e.g.*, spectinomycin), cephalosporins (*e.g.*, cephalexin), Colistin and Polymyxin B; Sulfonamides such as Co-trimoxazole, Trimethoprim Sulfisoxazole, Sulfamethoxazole, Sulfadiazine, Sulfamethizole and Sulfacetamide; Miscellaneous Antibacterial Agents such as Trimethoprim, Sulfamethazole, Chloramphenicol, Vancomycin, Metronidazole, Quinupristin, Dalfopristin, Rifampin, Spectinomycin, Sparsomycin, Nitrofurantoin; General Antiviral Agents such as Idoxuradine, Vidarabine, Trifluridine, Acyclovir, Famcyclovir, Penciclovir, Valacyclovir, Gancyclovir, Foscarnet, Ribavirin, Amantadine, Rimantadine, Cidofovir, Antisense Oligonucleotides, Immunoglobulins and Interferons; Drugs for HIV infection such as Tenofovir, Emtricitabine, Zidovudine, Didanosine, Zalcitabine, Stavudine, Lamivudine, Nevirapine, Delavirdine, Saquinavir, Ritonavir and Indinavir, Nelfinavir. Tetracycline antibiotics include, but are not limited to, tetracycline, chlortetracycline, oxytetracycline, demeclocycline, methacycline, sancycline, doxycycline, aureomycin, terramycin, minocycline, 6-deoxytetracycline, lymecycline, meclocycline, methacycline, rolitetracycline, and glycylicycline antibiotics (*e.g.*, tigecycline).

[0055] The term “neurological disease” refers to any disease of the nervous system, including diseases that involve the central nervous system (brain, brainstem and cerebellum), the peripheral nervous system (including cranial nerves), and the autonomic nervous system

(parts of which are located in both central and peripheral nervous system). Neurodegenerative diseases refer to a type of neurological disease marked by the loss of nerve cells, including, but not limited to, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, tauopathies (including frontotemporal dementia), and Huntington's disease. Examples of neurological diseases include, but are not limited to, headache, stupor and coma, dementia, seizure, sleep disorders, trauma, infections, neoplasms, neuro-ophthalmology, movement disorders, demyelinating diseases, spinal cord disorders, and disorders of peripheral nerves, muscle and neuromuscular junctions. Addiction and mental illness, include, but are not limited to, bipolar disorder and schizophrenia, are also included in the definition of neurological diseases. Further examples of neurological diseases include acquired epileptiform aphasia; acute disseminated encephalomyelitis; adrenoleukodystrophy; agenesis of the corpus callosum; agnosia; Aicardi syndrome; Alexander disease; Alpers' disease; alternating hemiplegia; Alzheimer's disease; amyotrophic lateral sclerosis; anencephaly; Angelman syndrome; angiomas; anoxia; aphasia; apraxia; arachnoid cysts; arachnoiditis; Arnold-Chiari malformation; arteriovenous malformation; Asperger syndrome; ataxia telangiectasia; attention deficit hyperactivity disorder; autism; autonomic dysfunction; back pain; Batten disease; Behcet's disease; Bell's palsy; benign essential blepharospasm; benign focal; amyotrophy; benign intracranial hypertension; Binswanger's disease; blepharospasm; Bloch Sulzberger syndrome; brachial plexus injury; brain abscess; brain injury; brain tumors (including glioblastoma multiforme); spinal tumor; Brown-Sequard syndrome; Canavan disease; carpal tunnel syndrome (CTS); causalgia; central pain syndrome; central pontine myelinolysis; cephalic disorder; cerebral aneurysm; cerebral arteriosclerosis; cerebral atrophy; cerebral gigantism; cerebral palsy; Charcot-Marie-Tooth disease; chemotherapy-induced neuropathy and neuropathic pain; Chiari malformation; chorea; chronic inflammatory demyelinating polyneuropathy (CIDP); chronic pain; chronic regional pain syndrome; Coffin Lowry syndrome; coma, including persistent vegetative state; congenital facial diplegia; corticobasal degeneration; cranial arteritis; craniosynostosis; Creutzfeldt-Jakob disease; cumulative trauma disorders; Cushing's syndrome; cytomegalic inclusion body disease (CIBD); cytomegalovirus infection; dancing eyes-dancing feet syndrome; Dandy-Walker syndrome; Dawson disease; De Morsier's syndrome; Dejerine-Klumpke palsy; dementia; dermatomyositis; diabetic neuropathy; diffuse sclerosis; dysautonomia; dysgraphia; dyslexia; dystonias; early infantile epileptic encephalopathy; empty sella syndrome; encephalitis; encephaloceles; encephalotrigeminal angiomas; epilepsy; Erb's

palsy; essential tremor; Fabry's disease; Fahr's syndrome; fainting; familial spastic paralysis; febrile seizures; Fisher syndrome; Friedreich's ataxia; frontotemporal dementia and other "tauopathies"; Gaucher's disease; Gerstmann's syndrome; giant cell arteritis; giant cell inclusion disease; globoid cell leukodystrophy; Guillain-Barre syndrome; HTLV-1 associated myelopathy; Hallervorden-Spatz disease; head injury; headache; hemifacial spasm; hereditary spastic paraplegia; hereditary ataxia polyneuritis; herpes zoster oticus; herpes zoster; Hirayama syndrome; HIV-associated dementia and neuropathy (see also neurological manifestations of AIDS); holoprosencephaly; Huntington's disease and other polyglutamine repeat diseases; hydranencephaly; hydrocephalus; hypercortisolism; hypoxia; immune-mediated encephalomyelitis; inclusion body myositis; incontinentia pigmenti; infantile; phytanic acid storage disease; Infantile Refsum disease; infantile spasms; inflammatory myopathy; intracranial cyst; intracranial hypertension; Joubert syndrome; Kearns-Sayre syndrome; Kennedy disease; Kinsbourne syndrome; Klippel Feil syndrome; Krabbe disease; Kugelberg-Welander disease; kuru; Lafora disease; Lambert-Eaton myasthenic syndrome; Landau-Kleffner syndrome; lateral medullary (Wallenberg) syndrome; learning disabilities; Leigh's disease; Lennox-Gastaut syndrome; Lesch-Nyhan syndrome; leukodystrophy; Lewy body dementia; lissencephaly; locked-in syndrome; Lou Gehrig's disease (aka motor neuron disease or amyotrophic lateral sclerosis); lumbar disc disease; Lyme disease-neurological sequelae; Machado-Joseph disease; macrencephaly; megalencephaly; Melkersson-Rosenthal syndrome; Meniere's disease; meningitis; Menkes disease; metachromatic leukodystrophy; microcephaly; migraine; Miller Fisher syndrome; mini-strokes; mitochondrial myopathies; Mobius syndrome; monomelic amyotrophy; motor neuron disease; moyamoya disease; mucopolysaccharidoses; multi-infarct dementia; multifocal motor neuropathy; multiple sclerosis and other demyelinating disorders; multiple system atrophy with postural hypotension; muscular dystrophy; myasthenia gravis; myelinoclastic diffuse sclerosis; myoclonic encephalopathy of infants; myoclonus; myopathy; myotonia congenita; narcolepsy; neurofibromatosis; neuroleptic malignant syndrome; neurological manifestations of AIDS; neurological sequelae of lupus; neuromyotonia; neuronal ceroid lipofuscinosis; neuronal migration disorders; Niemann-Pick disease; O'Sullivan-McLeod syndrome; occipital neuralgia; occult spinal dysraphism sequence; Ohtahara syndrome; olivopontocerebellar atrophy; opsoclonus myoclonus; optic neuritis; orthostatic hypotension; overuse syndrome; paresthesia; Parkinson's disease; paramyotonia congenita; paraneoplastic diseases; paroxysmal attacks; Parry Romberg syndrome; Pelizaeus-Merzbacher disease;

periodic paralyses; peripheral neuropathy; painful neuropathy and neuropathic pain; persistent vegetative state; pervasive developmental disorders; photic sneeze reflex; phytanic acid storage disease; Pick's disease; pinched nerve; pituitary tumors; polymyositis; porencephaly; Post-Polio syndrome; postherpetic neuralgia (PHN); postinfectious encephalomyelitis; postural hypotension; Prader-Willi syndrome; primary lateral sclerosis; prion diseases; progressive; hemifacial atrophy; progressive multifocal leukoencephalopathy; progressive sclerosing poliodystrophy; progressive supranuclear palsy; pseudotumor cerebri; Ramsay-Hunt syndrome (Type I and Type II); Rasmussen's Encephalitis; reflex sympathetic dystrophy syndrome; Refsum disease; repetitive motion disorders; repetitive stress injuries; restless legs syndrome; retrovirus-associated myelopathy; Rett syndrome; Reye's syndrome; Saint Vitus Dance; Sandhoff disease; Schilder's disease; schizencephaly; septo-optic dysplasia; shaken baby syndrome; shingles; Shy-Drager syndrome; Sjogren's syndrome; sleep apnea; Soto's syndrome; spasticity; spina bifida; spinal cord injury; spinal cord tumors; spinal muscular atrophy; stiff-person syndrome; stroke; Sturge-Weber syndrome; subacute sclerosing panencephalitis; subarachnoid hemorrhage; subcortical arteriosclerotic encephalopathy; sydenham chorea; syncope; syringomyelia; tardive dyskinesia; Tay-Sachs disease; temporal arteritis; tethered spinal cord syndrome; Thomsen disease; thoracic outlet syndrome; tic douloureux; Todd's paralysis; Tourette syndrome; transient ischemic attack; transmissible spongiform encephalopathies; transverse myelitis; traumatic brain injury; tremor; trigeminal neuralgia; tropical spastic paraparesis; tuberous sclerosis; vascular dementia (multi-infarct dementia); vasculitis including temporal arteritis; Von Hippel-Lindau Disease (VHL); Wallenberg's syndrome; Werdnig-Hoffman disease; West syndrome; whiplash; Williams syndrome; Wilson's disease; and Zellweger syndrome.

[0056] The term "metabolic disorder" refers to any disorder that involves an alteration in the normal metabolism of carbohydrates, lipids, proteins, nucleic acids, or a combination thereof. A metabolic disorder is associated with either a deficiency or excess in a metabolic pathway resulting in an imbalance in metabolism of nucleic acids, proteins, lipids, and/or carbohydrates. Factors affecting metabolism include, and are not limited to, the endocrine (hormonal) control system (*e.g.*, the insulin pathway, the enteroendocrine hormones including GLP-1, PYY or the like), the neural control system (*e.g.*, GLP-1 in the brain), or the like. Examples of metabolic disorders include, but are not limited to, diabetes (*e.g.*, Type I diabetes, Type II diabetes, gestational diabetes), hyperglycemia, hyperinsulinemia, insulin resistance, and obesity.

[0057] Immune disorders, such as auto-immune disorders, include, but are not limited to, arthritis (including rheumatoid arthritis, spondyloarthropathies, gouty arthritis, degenerative joint diseases such as osteoarthritis, systemic lupus erythematosus, Sjogren's syndrome, ankylosing spondylitis, undifferentiated spondylitis, Behcet's disease, haemolytic autoimmune anaemias, multiple sclerosis, amyotrophic lateral sclerosis, amylosis, acute painful shoulder, psoriatic, and juvenile arthritis), asthma, atherosclerosis, osteoporosis, bronchitis, tendonitis, bursitis, skin condition (*e.g.*, psoriasis, eczema, burns, dermatitis, pruritus (itch)), enuresis, eosinophilic disease, gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.*, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), and disorders ameliorated by a gastroprokinetic agent (*e.g.*, ileus, postoperative ileus and ileus during sepsis; gastroesophageal reflux disease (GORD, or its synonym GERD); eosinophilic esophagitis, gastroparesis such as diabetic gastroparesis; food intolerances and food allergies and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD) and non-cardiac chest pain (NCCP, including costo-chondritis)).

[0058] It will be appreciated that, in certain embodiments, each variable recited is as defined above and described in embodiments, herein, both singly and in combination.

[0059] The term "polymer" refers to a compound comprising eleven or more covalently connected repeating units. In certain embodiments, a polymer is naturally occurring. In certain embodiments, a polymer is synthetic (*i.e.*, not naturally occurring). The term "monomer" refers to the individual units which make up the polymer. Monomers included in the solid dosage forms, kits, and methods disclosed herein are those capable of polymerization when contacting oxygen released from an oxygen source by an endogenous catalyst *in vivo*. In some embodiments the monomer comprises dopamine, levodopa, norepinephrine, methyl dopa, levodopa methyl ester, levodopa ethyl ester, or a combination thereof. In some embodiments the monomer comprises dopamine. In some embodiments the monomer comprises levodopa. In some embodiments the monomer comprises norepinephrine. In some embodiments the monomer comprises methyl dopa. In some embodiments the monomer comprises levodopa methyl ester. In some embodiments the

monomer comprises levodopa ethyl ester. In some embodiments, the monomer further comprises a second molecule. In some embodiments the monomer comprises a backbone molecule. In some embodiments, the backbone molecule is covalently bound to the monomer. In some embodiments, the backbone molecule is selected from alginate, hyaluronic acid, polyacrylic acid, polyethylene glycol, chondroitin sulfate, chitosan, and combinations thereof. In some embodiments, the monomer is levodopa bound to alginate. In some embodiments, the monomer is dopamine bound to alginate.

[0060] The term “nanoparticle” refers to a particle having an average (*e.g.*, mean) dimension (*e.g.*, diameter) of between about 1 nanometer (nm) and about 1 micrometer (μm) (*e.g.*, between about 1 nm and about 300 nm, between about 1 nm and about 100 nm, between about 1 nm and about 30 nm, between about 1 nm and about 10 nm, or between about 1 nm and about 3 nm), inclusive.

[0061] As used herein, the term “assembly” or “assembling” refers to the formation of a polymer by covalent connection of repeating units. For example, a polymer may be assembled from any of the monomers disclosed herein.

[0062] As used herein, the term “agent” means a molecule, group of molecules, complex or substance administered to an organism for diagnostic, therapeutic, preventative medical, or veterinary purposes. In certain embodiments, the agent is an active pharmaceutical agent, a diagnostic agent, or a prophylactic agent). In certain embodiments, the solid oral dosage form disclosed herein comprise an agent(s), *e.g.*, a first agent (*e.g.*, at least one (including, *e.g.*, at least two, at least three). In some embodiments, the solid oral dosage form disclosed herein can further comprise a second agent. In some embodiments, the agent is an enzyme (*e.g.*, a digestive enzyme), a nutrient blocker (*e.g.*, a crosslinking agent), an aptamer, an antibody, a neutralizing agent, a diagnostic agent, a radioprotective agent, a nutraceutical, an active pharmaceutical agent, or a combination thereof.

[0063] In some embodiments, the active pharmaceutical agent is an antiparkinsonism therapeutic. Exemplary antiparkinsonism therapeutics include but are not limited to levodopa, amantadine, trihexyphenidyl, Entacapone, dopamine agonists (*i.e.*, carbidopa), bromocriptine, biperiden, pramipexole, selegiline, ropinirole, tolcapone, apomorphine, rotigotine, and procyclidine.

[0064] As used herein, the term “neutralizing agent” means an agent that neutralizes an acid or base. In some embodiments, the neutralizing agent is an acid. In some embodiments, the neutralizing agent is a base. In certain embodiments, the neutralizing agent is a buffer.

[0065] As used herein, the term “diagnostic agent” means an imaging agent or contrast agent. The terms “imaging agent” and “contrast agent” refer to a substance used to enhance the contrast of structures or fluids within the body in medical imaging. It is commonly used to enhance the visibility of blood vessels and the gastrointestinal tract in medical imaging.

[0066] As used herein, the term “active pharmaceutical agent” includes an agent that is capable of providing a local or systemic biological, physiological, or therapeutic effect in the biological system to which it is applied. For example, an active pharmaceutical agent can act to control tumor growth, control infection or inflammation, act as an analgesic, promote anti-cell attachment, and enhance bone growth, among other functions. Other suitable active pharmaceutical agents can include anti-viral agents, hormones, antibodies, therapeutic proteins, or prophylactics. Other active pharmaceutical agents include prodrugs, which are agents that are not biologically active when administered but, upon administration to a subject are converted to biologically active agents through metabolism or some other mechanism.

[0067] An active pharmaceutical agent can be a compound, *e.g.*, small organic or inorganic molecules; saccharines; oligosaccharides; polysaccharides; biological macromolecule, *e.g.*, peptides, proteins, and peptide analogs and derivatives; peptidomimetics; antibodies and antigen binding fragments thereof; nucleic acids; nucleic acid analogs and derivatives; an extract made from biological materials such as bacteria, plants, fungi, or animal cells; animal tissues; naturally occurring or synthetic compositions; and any combinations thereof.

[0068] Examples of active pharmaceutical agents include, but are not limited to, antimicrobial agents, analgesics, antiinflammatory agents, counterirritants, coagulation modifying agents, diuretics, sympathomimetics, anorexics, antacids and other gastrointestinal agents; antiparasitics, antidepressants, anti-hypertensives, anticholinergics, stimulants, antihormones, central and respiratory stimulants, drug antagonists, lipid-regulating agents, uricosurics, cardiac glycosides, electrolytes, ergot and derivatives thereof, expectorants, hypnotics and sedatives, antidiabetic agents, dopaminergic agents, antiemetics, muscle relaxants, para-sympathomimetics, anticonvulsants, antihistamines, beta-blockers, purgatives, antiarrhythmics, contrast materials, radiopharmaceuticals, antiallergic agents, tranquilizers, vasodilators, antiviral agents, and antineoplastic or cytostatic agents or other agents with anti-cancer properties, or a combination thereof. Other suitable active pharmaceutical agents include contraceptives and vitamins as well as micro- and macronutrients. Still other examples include antiinfectives such as antibiotics and antiviral agents; analgesics and

analgesic combinations; anorexics; antiheimintics; antiarthritics; antiasthmatic agents; anticonvulsants; antidepressants; antidiuretic agents; antidiarrheals; antihistamines; anti-inflammatory agents; antimigraine preparations; antinauseants; antineoplastics; antiparkinsonism drugs; pain-management drugs, antipruritics; antipsychotics; antipyretics, antispasmodics; anticholinergics; sympathomimetics; xanthine derivatives; cardiovascular preparations including calcium channel blockers and beta-blockers such as pindolol and antiarrhythmics; anti-hypertensives; diuretics; vasodilators including general coronary, peripheral and cerebral; central nervous system stimulants; cough and cold preparations, including decongestants; hormones such as estradiol and other steroids, including corticosteroids; hypnotics; immunosuppressives; muscle relaxants; parasympatholytics; psychostimulants; sedatives; and tranquilizers; and naturally derived or genetically engineered proteins, polysaccharides, glycoproteins, or lipoproteins. The disclosure is not intended to be limited in any manner by the above exemplary terms. Additional terms may be defined in other sections of this disclosure.

[0069] Exemplary active pharmaceutical agents include, but are not limited to, antibiotics, anti-viral agents, anesthetics, anti-coagulants, inhibitors of an enzyme, steroidal agents, steroidal or non-steroidal anti-inflammatory agents, antihistamine, immunosuppressant agents, antigens, vaccines, antibodies, decongestant, sedatives, opioids, pain-relieving agents, analgesics, anti-pyretics, hormones, and prostaglandins, *etc.* Active pharmaceutical agent include small organic molecules such as drug compounds (*e.g.*, compounds approved by the US Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins and cells.

[0070] The term “gel” is a nonfluid colloidal network or nonfluid polymer network that is expanded throughout its whole volume by a fluid (*e.g.*, a solvent, such as water). A gel has a finite, usually rather small, yield stress. A gel may contain: (i) a covalent molecular network (*e.g.*, polymer network), *e.g.*, a network formed by crosslinking molecules (*e.g.*, polymers) or by nonlinear polymerization; (ii) a molecular network (*e.g.*, polymer network) formed through non-covalent aggregation of molecules (*e.g.*, polymers), caused by complexation (*e.g.*, coordination bond formation), electrostatic interactions, hydrophobic interactions,

hydrogen bonding, van der Waals interactions, π - π stacking, or a combination thereof, that results in regions of local order acting as the network junction points. The term “thermoreversible gel” refers to a gel where the regions of local order in the gel are thermally reversible; (iii) a polymer network formed through glassy junction points, *e.g.*, one based on block copolymers. If the junction points are thermally reversible glassy domains, the resulting swollen network may also be termed a thermoreversible gel; (iv) lamellar structures including mesophases, *e.g.*, soap gels, phospholipids, and clays; or (v) particulate disordered structures, *e.g.*, a flocculent precipitate usually consisting of particles with large geometrical anisotropy, such as in V_2O_5 gels and globular or fibrillar protein gels. The term “hydrogel” refers to a gel, in which the fluid is water.

[0071] The term “catalysis,” “catalyze,” or “catalytic” refers to the increase in rate of a chemical reaction due to the participation of a substance called a “catalyst.” In certain embodiments, the amount and nature of a catalyst remains essentially unchanged during a reaction. In certain embodiments, a catalyst is regenerated, or the nature of a catalyst is essentially restored after a reaction. A catalyst may participate in multiple chemical transformations. The effect of a catalyst may vary due to the presence of other substances known as inhibitors or poisons (which reduce the catalytic activity) or promoters (which increase the activity). Catalyzed reactions have lower activation energy (rate-limiting free energy of activation) than the corresponding uncatalyzed reaction, resulting in a higher reaction rate at the same temperature. Catalysts may affect the reaction environment favorably, bind to the reagents to polarize bonds, form specific intermediates that are not typically produced by an uncatalyzed reaction, or cause dissociation of reagents to reactive forms. In certain embodiments, the catalyst is present on a tissue. In some embodiments, the catalyst is present in a tissue.

[0072] The term “carrier” and “excipient”, are used interchangeably herein and refer to an inert substrate which houses the active pharmaceutical agent within the dosage form. Exemplary carriers include but are not limited to sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such

as, for example, cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, (i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof, and (j) drug release matrixes.

[0073] The term “drug release matrix” refers to an inert substrate which houses the active pharmaceutical and allows for the time-controlled release of the active pharmaceutical. Exemplary drug release matrixes include but are not limited hydroxypropyl methyl cellulose (HPMC), polycaprolactone (PCL), hydroxypropyl cellulose (HPC), acrylate copolymers (including copolymers of ethyl acrylate and methyl methacrylate, and Eudragit® RS100 and Eudragit® RL-PO (ethyl acrylate/methyl acrylate copolymers with low content of methacrylic acid ester with quaternary ammonium groups), , and ethyl cellulose (EC).

[0074] The term “small molecule” refers to molecules, whether naturally-occurring or artificially created (*e.g.*, via chemical synthesis) that have a relatively low molecular weight. Typically, a small molecule is an organic compound (*e.g.*, it contains carbon). The small molecule may contain multiple carbon-carbon bonds, stereocenters, and other functional groups (*e.g.*, amines, hydroxyl, carbonyls, and heterocyclic rings, *etc.*). In certain embodiments, the molecular weight of a small molecule is not more than about 1,000 g/mol, not more than about 900 g/mol, not more than about 800 g/mol, not more than about 700 g/mol, not more than about 600 g/mol, not more than about 500 g/mol, not more than about 400 g/mol, not more than about 300 g/mol, not more than about 200 g/mol, or not more than about 100 g/mol. In certain embodiments, the molecular weight of a small molecule is at least about 100 g/mol, at least about 200 g/mol, at least about 300 g/mol, at least about 400 g/mol, at least about 500 g/mol, at least about 600 g/mol, at least about 700 g/mol, at least about 800 g/mol, or at least about 900 g/mol, or at least about 1,000 g/mol. Combinations of the above ranges (*e.g.*, at least about 200 g/mol and not more than about 500 g/mol) are also possible. In certain embodiments, the small molecule is a therapeutically active agent such as a drug (*e.g.*, a molecule approved by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (C.F.R.)). The small molecule may also be complexed with one or more metal atoms and/or metal ions. In this instance, the small molecule is also referred to as a “small organometallic molecule.” Preferred small molecules are biologically active in that they produce a biological effect in animals, preferably mammals, more preferably humans. Small molecules include, but are not limited to, radionuclides and imaging agents. In certain embodiments, the small molecule is a drug. Preferably, though not necessarily, the drug is

one that has already been deemed safe and effective for use in humans or animals by the appropriate governmental agency or regulatory body. For example, drugs approved for human use are listed by the FDA under 21 C.F.R. §§ 330.5, 331 through 361, and 440 through 460, incorporated herein by reference; drugs for veterinary use are listed by the FDA under 21 C.F.R. §§ 500 through 589, incorporated herein by reference. All listed drugs are considered acceptable for use in accordance with the present disclosure.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0075] Patient compliance and therefore therapeutic efficacy can often depend on one another. It has been shown that therapeutics which require multiple doses a day, due to an abbreviated half-life, result in lower patient compliance and thus limited treatment efficacy. The unexpected discovery by the inventors of the solid oral dosage form, methods, and kits disclosed herein mitigates these issues, allowing for extension of the residence time of active pharmaceutical agents *in vivo*. In particular, the solid oral dosage forms, methods, and kits disclosed herein are particularly useful for drugs that require more than once daily administration. Similarly, the solid oral dosage forms, methods, and kits disclosed herein are particularly useful for drugs that have short half-lives.

[0076] Two therapeutic areas that stand to benefit significantly from improved patient adherence are infectious diseases and Parkinson's disease (PD). Antibiotics are used to treat a wide variety of infections and decreasing the frequency of administration stands to have a positive impact on adherence. The case is similar for treatments for Parkinson's disease, where treatments are essential in supporting and maximizing neurologic motor function. Poor adherence to anti-infective therapy may lead to therapeutic failure, re-infection, and resistance. For example, in a study analyzing treatment outcomes of patients treated with suspected bacterial infections of the lower respiratory tract, pharyngitis and dental infections, patients in the twice-daily groups had a higher bacteriologic failure rate in comparison to the once-daily group (7.1% vs 2.8% for the once-daily group).^[3-5]

[0077] PD resulted in 3.2 million (95% uncertainty interval (UI) 2.6–4.0) disability-adjusted life-years (DALYs) and 211,296 deaths (95% UI 167771–265160) in 2016.^[6] More than one third of PD patients, who despite taking three or more daily drug doses, experience severe motor fluctuations, fatigue, cognitive impairment and/or mood disturbances. This leads to reported low adherence to their pharmacotherapy.^[7, 8] To solve these problems and increase

patient adherence, there is a need to develop orally-delivered sustained release platforms that can reduce dosing frequency and simplify drug administration.

[0078] Gastric resident drug delivery systems have previously been developed and their utility for the delivery of anti-infective and contraceptive drugs has been demonstrated.^[10-15] However, these systems are limited by the volume that is encapsulated in an ingestible capsule, and accordingly are not useful for drugs which require significant daily dosages, such as antibiotics and drugs for the treatment of PD.

[0079] The inventors unexpectedly discovered a solution to these problems by way of the solid oral dosage forms, methods and kits disclosed herein. In particular, the inventors utilize an enzyme-triggered small intestinal targeting adhesion technology termed gastrointestinal synthetic epithelial lining (GSEL)^[36] to develop the solid oral dosage forms disclosed herein. In some embodiments, GSEL enables strong tissue adhesion through intestinal catalase (CAT) catalyzed polymerization of dopamine (DA) to poly(dopamine) (PDA). *In situ* oxidation of catechol groups (such as in dopamine) to quinones leads to covalent crosslinking and adhesion to biological substrates.^[55] Moreover, quinone can also react with various nucleophilic functional groups (i.e., –NH₂, –SH, imidazole) exposed on different types of tissue surfaces, via Michael type addition or Schiff base reaction, thus leading to the formation of covalent bonds.^[37, 38] Mussel-inspired adhesives applied to the oral drug delivery have yet to be clinically translated, due to some challenges, particularly with respect to practical load-bearing applications. For example, the stomach seems to have a limited capacity of absorption and may decarboxylate levodopa. Moreover, large intestinal microbiota can dehydroxylate levodopa to dopamine,^[56] which increases the dosage regimen of levodopa treatment in PD. It has a pivotal role in regulating the delivery of the ingested levodopa dose to the proximal small bowel, where most of the levodopa absorption takes place.^[57] By relying on *in situ* intestinal enzyme-responsive components with an ultrafast and robust response, the inventors have enabled the development of a new generation of GI bio-adhesive platforms.

[0080] Therefore, based on the mechanism for specific targeting and localization to the small intestine of the developed GSEL system, the inventors synthesized as one embodiment, catechol-functionalized polymers, modifying alginate (ALG) backbones with DA (ALG-DA). Mixing the ALG-DA with other GSEL ingredients enables gelation on the surface of the small intestine due to the presence of the enzyme – CAT to form a 3D hydrogel system. The oxidized catechol groups of DA covalently react with biomolecules on the small intestine,

making a robust adhesion in the hydrated intestinal environment. Without wishing to be bound by theory, the inventors posit that dopamine in alginate-dopamine is localized at the surface to provide adhesion, while the alginate is crosslinked to provide bulk cohesion. PDA also links everything together, and the components diffuse and harden to form the final hydrogel.

[0081] The inventors employed this technology in a multi-layered pill including at least one layer capable of forming an adhesive hydrogel and a drug reservoir layer. In developing this platform, the inventors overcame several barriers. First, large drug loading may influence the adhesion of the polymer. Second, the other excipients' contents may influence the gelling homogenization. To address the dose loading challenge, a multi-layered pill was designed where the drug layer was able to load and release various drugs and the monomer layer was mixed with ingredients that react homogeneously to support mucosal adhesion via hydrogel formation. However, hydrogels can be fragile, which may limit their use in most load-bearing applications. To ensure the systems could be stored under dry conditions, all components were blended in a dry powder form, which then interact, gel, and form the final adhesive when in contact with moist tissue. For the drug layer, drugs can be encapsulated in polymer matrices. These formulations released drug with a profile with near zero-order release kinetics.

[0082] The drug reservoir layer is capable of supporting hydrophilic and hydrophobic drugs. The inventors surprisingly discovered that such the solid oral dosage forms remain intact until they reach the small intestine, where polymerization takes place, allowing for extended release of the drug at this physiological location. The data disclosed herein demonstrate utility of this intestine-specific resident drug delivery system in a large animal model. This platform has the ability to load and release drugs in a controlled and sustained manner and can be applied towards a broad set of active pharmaceutical ingredients.

[0083] The aspects described herein are not limited to specific embodiments, systems, dosage forms, methods, or configurations, and as such can, of course, vary. The terminology used herein is for the purpose of describing particular aspects only and, unless specifically defined herein, is not intended to be limiting.

[0084] In one aspect, provided herein a solid oral dosage form comprising a first layer and a second layer wherein the first layer comprises a monomer and an oxygen source; the second layer comprises an active pharmaceutical agent; and the monomer further comprises a backbone molecule.

[0085] In some embodiments, the solid oral dosage form disclosed herein, further comprising a third layer, wherein: the third layer comprises a monomer and an oxygen source; and the second layer is disposed between the first and the third layer. In some embodiments, there are more than three layers. In some embodiments, there are more than four layers. In some embodiments, there are more than five layers.

[0086] In certain embodiments, the monomer and the oxygen source of the first layer are the same as the monomer and the oxygen source of the third layer. In certain embodiments, the monomer and the oxygen source of the first layer are different than the monomer and the oxygen source of the third layer.

[0087] In some embodiments, the monomer is a catechol-based monomer. In some embodiments, the monomer comprises a 1,2-dihydroxybenzene moiety. In some embodiments, the monomer comprises an optionally substituted 1,2-dihydroxybenzene moiety. In some embodiments, the monomer comprises 1,2-dihydroxyphenyl. In some embodiments, the monomer comprises an optionally substituted 1,2-dihydroxyphenyl.

[0088] In some embodiments, the monomer is a 2-(3,4-dihydroxyphenyl)ethylamine-based monomer. In certain embodiments, the monomer comprises a 3,4-dihydroxyphenethylamine moiety. In certain embodiments, the monomer comprises an optionally substituted 3,4-dihydroxyphenethylamine moiety. In certain embodiments, the monomer comprises 2-(3,4-dihydroxyphenyl)ethylamine. In certain embodiments, the monomer comprises an optionally substituted 2-(3,4-dihydroxyphenyl)ethylamine moiety.

[0089] In some embodiments, the monomer comprises dopamine, levodopa, norepinephrine, methyl dopa, levodopa methyl ester, levodopa ethyl ester, or a combination thereof. In some embodiments, the monomer is selected from the group consisting of dopamine, levodopa, norepinephrine, methyl dopa, levodopa methyl ester, levodopa ethyl ester, derivatives thereof, and combinations thereof. In certain embodiments, the monomer comprises dopamine. In certain embodiments, the monomer comprises levodopa. In certain embodiments, the monomer comprises norepinephrine. In certain embodiments, the monomer comprises methyl dopa. In certain embodiments, the monomer comprises levodopa methyl ester. In certain embodiments, the monomer comprises levodopa ethyl ester. In some embodiments, the monomer comprises dopamine, levodopa, norepinephrine, methyl dopa, levodopa methyl ester, or levodopa ethyl ester and at least one backbone molecule.

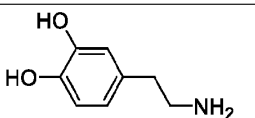
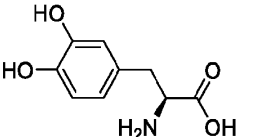
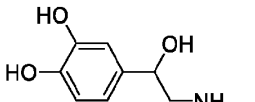
[0090] In some embodiments, the backbone molecule comprises alginate, hyaluronic acid, polyacrylic acid, polyethylene glycol, chondroitin sulfate, chitosan, or a combination thereof.

In certain embodiments, the backbone molecule comprises alginate. In some embodiments, the backbone molecule consists of alginate of a variant thereof. In some embodiments, the backbone molecule consists of hyaluronic acid or a variant thereof. In some embodiments, the backbone molecule consists of polyacrylic acid or a variant thereof. In some embodiments, the backbone molecule consists of polyethylene glycol or a variant thereof. In some embodiments, the backbone molecule consists of chondroitin sulfate or a variant thereof. In some embodiments, the backbone molecule consists of chitosan of a variant thereof.

[0091] In some embodiments, monomer is covalently bound to the backbone molecule. In certain embodiments the monomer comprises (A) dopamine, levodopa, norepinephrine, methyldopa, levodopa methyl ester, or levodopa ethyl ester moieties bound to (B) alginate, hyaluronic acid, polyacrylic acid, polyethylene glycol, chondroitin sulfate, or chitosan. In certain embodiments the monomer comprises (A) more than one of dopamine, levodopa, norepinephrine, methyldopa, levodopa methyl ester, and levodopa ethyl ester moieties bound to (B) alginate, hyaluronic acid, polyacrylic acid, polyethylene glycol, chondroitin sulfate, or chitosan. In certain embodiments the monomer comprises (A) more than one of dopamine, levodopa, norepinephrine, methyldopa, levodopa methyl ester, and levodopa ethyl ester moieties bound to (B) more than one of alginate, hyaluronic acid, polyacrylic acid, polyethylene glycol, chondroitin sulfate, and chitosan.

[0092] In certain embodiments, the monomer is selected from the structures listed in Table 1 or 2.

Table 1: Monomers

Monomer	Structure
M1	
M2	
M3	

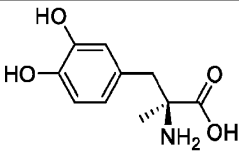
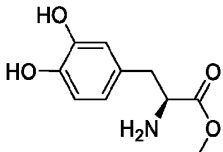
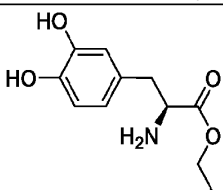
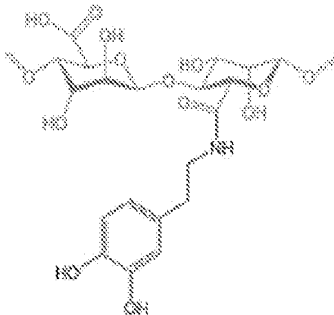
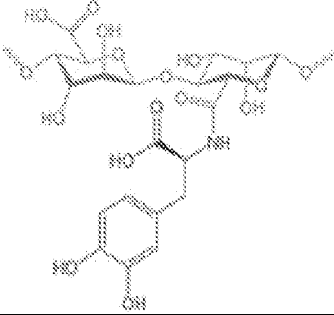
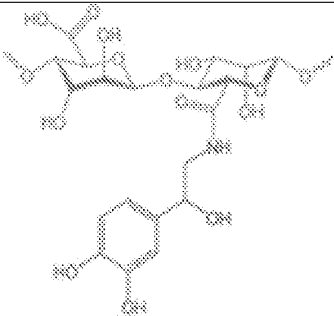
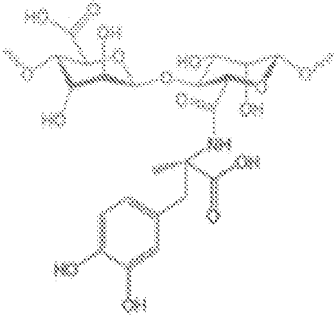
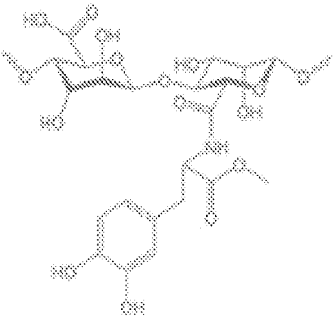
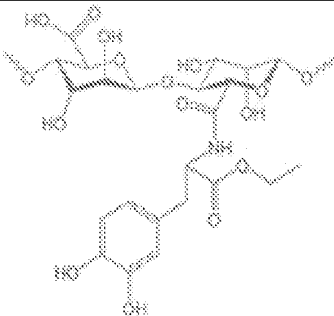
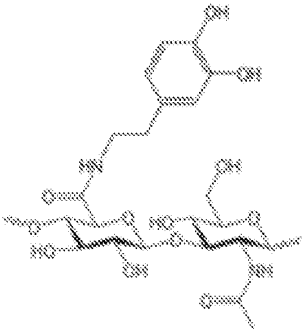
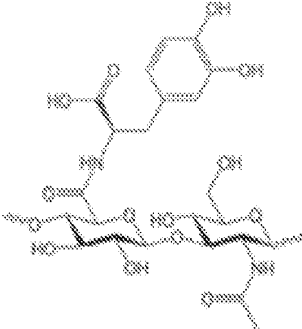
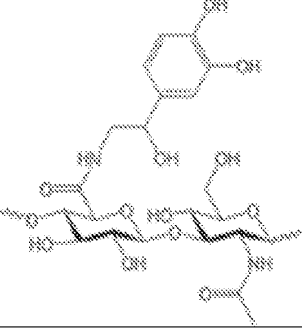
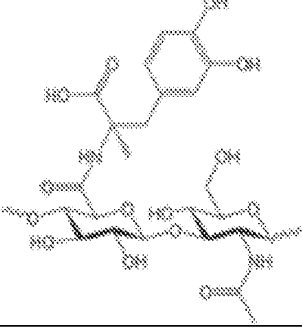
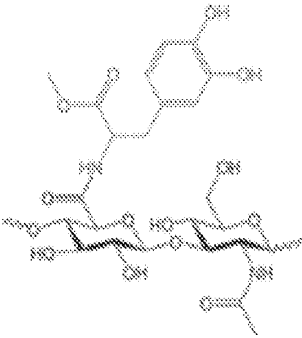
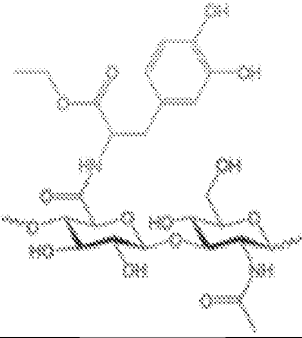
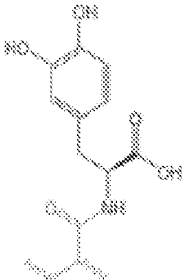
Monomer	Structure
M4	
M5	
M6	

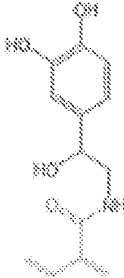
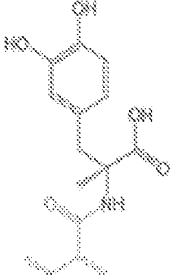
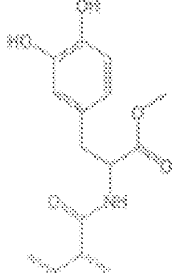
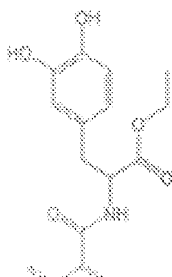
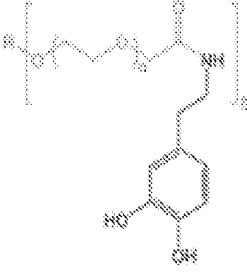
Table 2: Macromolecules

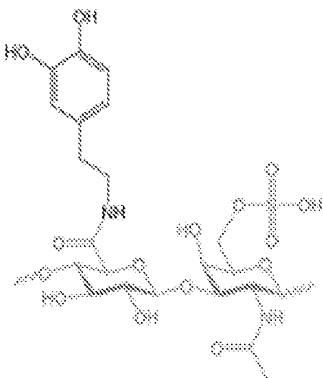
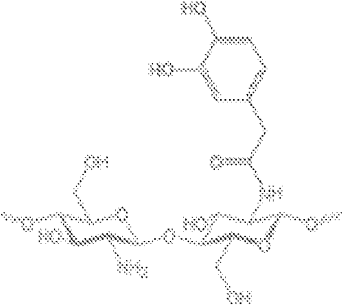
Macromolecule	Components	Structure
C1	M1 and alginate	
C2	M2 and alginate	

Macromolecule	Components	Structure
C3	M3 and alginate	
C4	M4 and alginate	
C5	M5 and alginate	
C6	M6 and alginate	

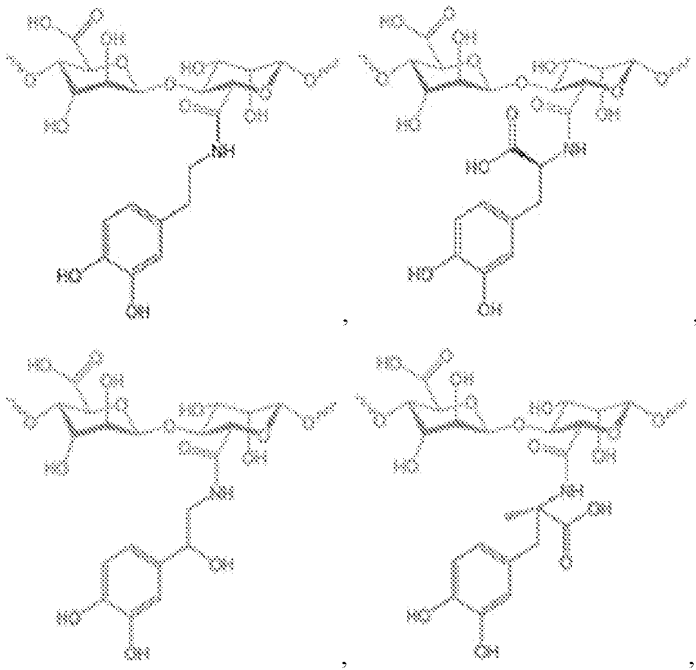
Macromolecule	Components	Structure
C7	M1 and hyaluronic acid	
C8	M2 and hyaluronic acid	
C9	M3 and hyaluronic acid	
C10	M4 and hyaluronic acid	

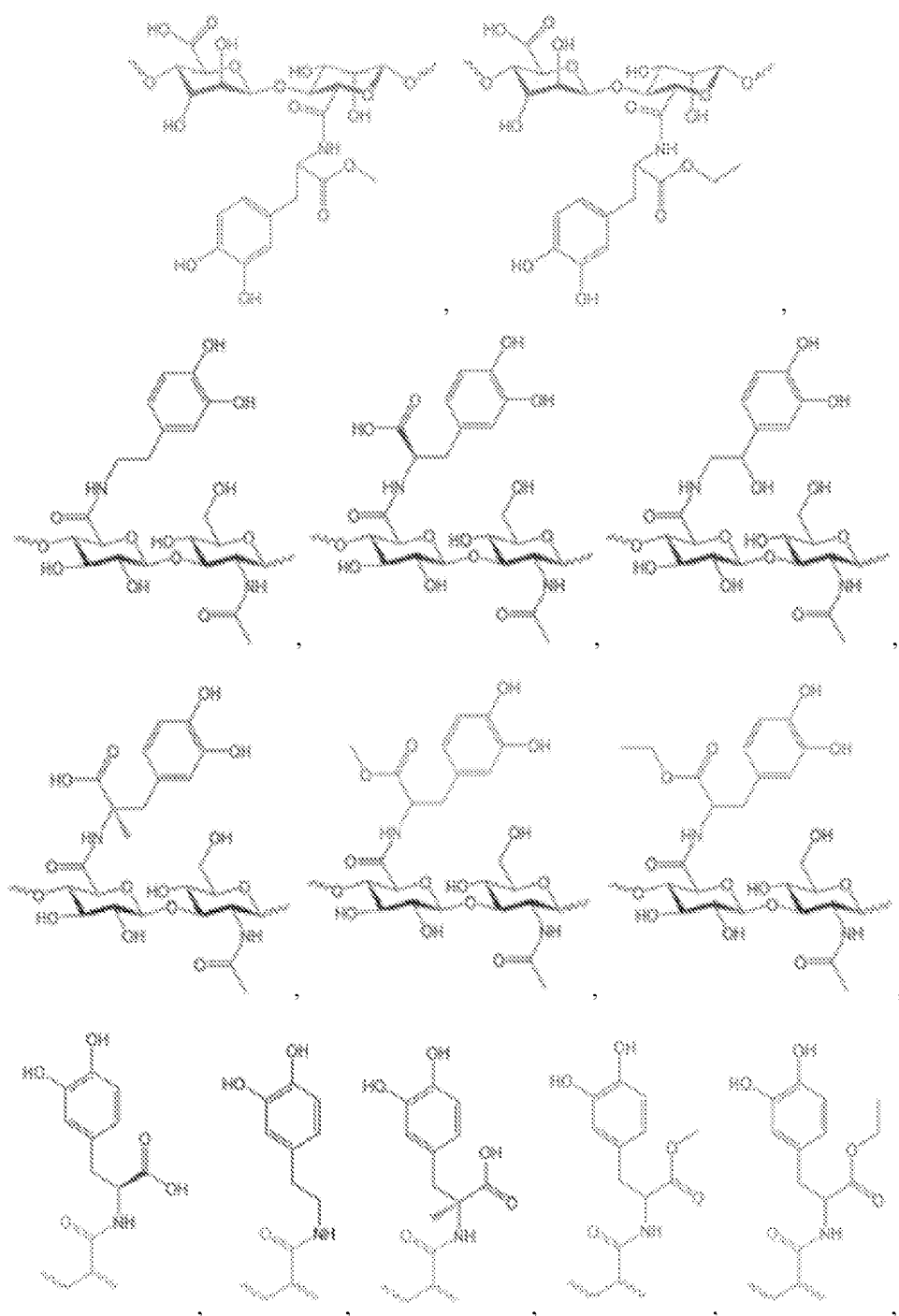
Macromolecule	Components	Structure
C11	M5 and hyaluronic acid	
C12	M6 and hyaluronic acid	
C13	M1 and polyacrylic acid	
C14	M2 and polyacrylic acid	

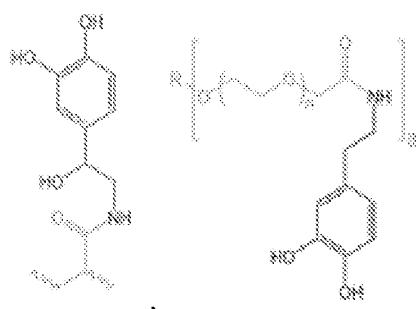
Macromolecule	Components	Structure
C15	M3 and polyacrylic acid	
C16	M4 and polyacrylic acid	
C17	M5 and polyacrylic acid	
C18	M6 and polyacrylic acid	
C19	M1 and polyethylene with tripentaerythritol core	 R=tripentaerythritol core structure

Macromolecule	Components	Structure
C20	M1 and chondroitin sulfate	
C21	M1 and chitosan	

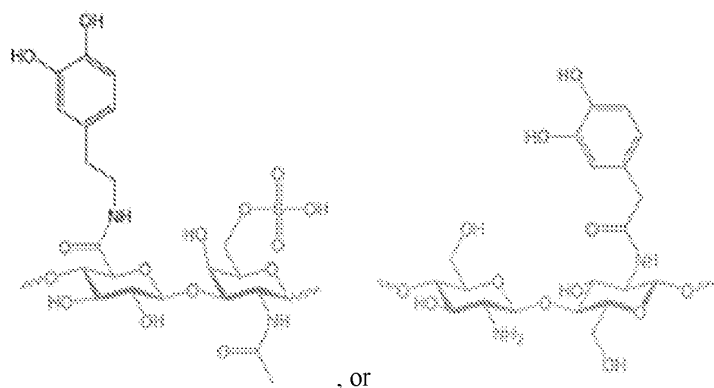
[0093] In certain embodiments, the monomer is of the formula:



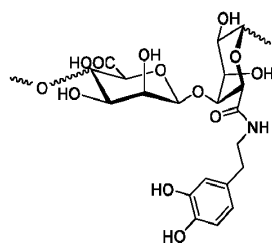




wherein R comprises a moiety derived from tripentaerythritol,



[0094] In certain embodiments, the monomer comprises dopamine and the backbone molecule comprises alginate. In some embodiments, the monomer is of the formula:



[0095] In some embodiments, the ratio of monomer to macromolecule used in the conjugation of these two species is about 10:1 to about 1:10. In some embodiments, the ratio is about 5:1 to about 1:5. In some embodiments, the ratio is about 2:1 to about 1:2. In some embodiments, the ratio is about 1:1 to about 1:2. In some embodiments, the ratio is about 1:1. In some embodiments, the ratio is about 1:2. In some embodiments, the ratio is about 2:1. In some embodiments, the ratio is about 4:1. In some embodiments, the ratio is about 1:4. In some embodiments, the ratio is about 3:1. In some embodiments, the ratio is about 1:3.

[0096] In certain embodiments, the monomer consists of a single type of monomer. In some embodiments, the monomer comprises a combination of monomers. In some embodiments, the combination of monomers consists of two or three different monomers. In certain embodiments, the monomer comprises a combination of monomers listed in Tables 1 and 2. In some embodiments, the combination of monomers consists of two different monomers. In some embodiments, the combination of monomers consists of three different monomers. In some embodiments, the combination of monomers consists of four different monomers.

[0097] In certain embodiments, the oxygen source is hydrogen peroxide or urea hydrogen peroxide. In some embodiments, the oxygen source is hydrogen peroxide. In some embodiments, the oxygen source is urea hydrogen peroxide.

[0098] In certain embodiments, the active pharmaceutical agent is a small molecule. In certain embodiments, the active pharmaceutical agent is a polypeptide. In certain embodiments, the active pharmaceutical agent is a nucleic acid construct. In certain embodiments, the active pharmaceutical agent is an antibody.

[0099] In some embodiments, the active pharmaceutical agent is used to treat an infectious disease, a neurological disease, a pain disorder, a proliferative disease, an autoimmune disease, an inflammatory disease, a metabolic disease, enzymatic deficiency, an immune disorder, or allergies. In some embodiments, the active pharmaceutical agent is used to treat a neurological disease. In some embodiments, the active pharmaceutical agent is used to treat a pain disorder. In some embodiments, the active pharmaceutical agent is used to treat a proliferative disease. In some embodiments, the active pharmaceutical agent is used to treat an autoimmune disease. In some embodiments, the active pharmaceutical agent is used to treat an inflammatory disease. In some embodiments, the active pharmaceutical agent is used to treat a metabolic disease. In some embodiments, the active pharmaceutical agent is used to treat enzymatic deficiency. In some embodiments, the active pharmaceutical agent is used to treat an immune disorder. In some embodiments, the active pharmaceutical agent is used to treat allergies. In some embodiments, the active pharmaceutical agent treats an infectious disease.

[00100] In some embodiments, the active pharmaceutical agent is an antiparasitic drug. In some embodiments, the active pharmaceutical agent is an anthelmintic drug. In some embodiments, the active pharmaceutical agent is praziquantel. In some embodiments, the active pharmaceutical agent is an antiviral drug. In some embodiments, the active pharmaceutical agent treats influenza. In some embodiments, the active pharmaceutical agent

treats SARS-CoV-2. In certain embodiments, the active pharmaceutical ingredient is a contraceptive, a statin, an anti-hypertensive, or an antibiotic. In some embodiments, the active pharmaceutical agent treats psychiatric disorders, Alzheimer's disease, infection diseases, or transplant rejection.

[00101] In some embodiments, the active pharmaceutical agent treats type 2 diabetes. In some embodiments, the active pharmaceutical agent treats non-alcoholic fatty liver disease. In some embodiments, the active pharmaceutical agent treats nonalcoholic steatohepatitis. In some embodiments, the active pharmaceutical agent treats ocular diseases. In some embodiments, the active pharmaceutical agent treats Crohn's disease. In some embodiments, the active pharmaceutical agent treats osteoarthritis. In some embodiments, the active pharmaceutical agent treats Alzheimer's disease. In some embodiments, the active pharmaceutical agent is a prophylactic.

[00102] In certain embodiments, the infectious disease is a bacterial infection. In some embodiments, the infectious disease is a viral infection. In some embodiments, the infectious disease is a parasitic infection. In some embodiments, the infectious disease is a protozoological infection.

[00103] In certain embodiments, the proliferative disease is cancer. In some embodiments, the neurological disease is a degenerative disease. In some embodiments, the neurological disease is Parkinson's disease, Alzheimer's disease, Huntington's disease, Lewy body disease, Prion disease, Moto neuron disease, Multiple sclerosis, Amyotrophic lateral sclerosis, Kippel-Feil syndrome, Leigh syndrome, or Striatonigral degeneration. In some embodiments, the neurological disease is Parkinson's disease.

[00104] In some embodiments, the active pharmaceutical agent is an anti-cancer agent. In certain embodiments, the active pharmaceutical agent is an anti-proliferative agent. In certain embodiments, the active pharmaceutical agent is an anti-cancer agent. In certain embodiments, the active pharmaceutical agent is an anti-viral agent.

[00105] In certain embodiments, the active pharmaceutical agent is selected from the group including, but not limited to, anti-proliferative agents, anti-cancer agents, anti-angiogenesis agents, steroidal or non-steroidal anti-inflammatory agents, immunosuppressants, anti-bacterial agents, anti-viral agents, cardiovascular agents, cholesterol-lowering agents, anti-diabetic agents, anti-allergic agents, contraceptive agents, and pain-relieving agents, anesthetics, anti-coagulants, inhibitors of an enzyme, steroidal agents, steroidal or antihistamine, antigens, vaccines, antibodies, decongestant, sedatives, opioids, analgesics,

anti-pyretics, hormones, and prostaglandins. In certain embodiments, the active pharmaceutical agent is an antibiotic.

[00106] In certain embodiments, the active pharmaceutical is an antibiotic or antiparkinsonism therapeutic. In some embodiments, the antiparkinsonism therapeutic comprises levodopa and carbidopa.

[00107] In certain embodiments, the antibiotic is a penicillin. In some embodiments, the antibiotic is Penicillin G, Penicillin V, Cloxacillin, Dicloxacillin, Methicillin, Nafcillin, Oxacillin, Ampicillin, moxycillin, Bacampicillin, Azlocillin, Carbenicillin, Mezlocillin, Piperacillin, Amoxicillin, or Ticarcillin. In some embodiments, the antibiotic is amoxicillin.

[00108] In certain embodiments, the active pharmaceutical agent has a half-life of less than 24 hours. In certain embodiments, the active pharmaceutical agent has a half-life of less than 16 hours. In some embodiments, the active pharmaceutical agent has a half-life of less than 12 hours. In some embodiments, the active pharmaceutical agent has a half-life of less than 6 hours. In some embodiments, the active pharmaceutical agent has a half-life of less than 3 hours. In some embodiments, the active pharmaceutical agent has a half-life of less than 2 hours. In some embodiments, the active pharmaceutical agent has a half-life of less than 1 hour.

[00109] In some embodiments, the active pharmaceutical agent has a half-life of between 1 and 4 hours. In some embodiments, the active pharmaceutical agent has a half-life of between 1 and 6 hours. In some embodiments, the active pharmaceutical agent has a half-life of between 5 and 10 hours. In some embodiments, the active pharmaceutical agent has a half-life of between 6 and 12 hours. In some embodiments, the active pharmaceutical agent has a half-life of between 6 and 18 hours. In some embodiments, the active pharmaceutical agent has a half-life of between 18 and 24 hours.

[00110] In some embodiments, the active pharmaceutical agent is dosed more frequently than once per day. In some embodiments, the active pharmaceutical agent is dosed more frequently than twice per day. In some embodiments, the active pharmaceutical agent is dosed more frequently than thrice per day. In some embodiments, the active pharmaceutical agent is dosed more frequently than four times per day.

[00111] In some embodiments, the first and third layers further comprise a buffer. In some embodiments, the buffer is tris base. In some embodiments, the ratio of monomer:Tris base:H₂O₂ is about 1:1.21:0.09. In some embodiments, the ratio of monomer:Tris base:H₂O₂ ranges from about 0.9:0.5:0.09 to 2:1.5:0.2. In some embodiments, the ratio of monomer:Tris

base:H₂O₂ ranges from about 1:0.9:0.09 to 2:1.5:0.2. In some embodiments, the ratio of monomer:Tris base:H₂O₂ ranges from about 0.5:1:0.05 to 2:1:0.2.

In some embodiments, the second layer further comprises a drug release matrix. In certain embodiments, the drug release matrix is selected to provide release of the drug for approximately 24 hours after administration. In certain embodiments, the drug release matrix is selected to provide release of the drug for approximately 48 hours after administration. In certain embodiments, the drug release matrix is selected to provide release of the drug for approximately 36 hours after administration. In certain embodiments, the drug release matrix is selected to provide release of the drug for approximately 12 hours after administration. In some embodiments, the drug release matrix controls the release of the active pharmaceutical. In some embodiments, the drug release matrix is selected from the group consisting of hydroxypropyl methyl cellulose (HPMC), polycaprolactone (PCL), hydroxypropyl cellulose (HPC), ethyl acrylate/methyl methacrylate copolymers, and ethyl cellulose (EC). In some embodiments, the drug release matrix is polycaprolactone (PCL). In some embodiments, the drug release matrix is hydroxypropyl cellulose (HPC). In some embodiments, the drug release matrix is a copolymer of ethyl acrylate and methyl methacrylate. In some embodiments, the drug release matrix is Eudragit® RS100. In some embodiments, the drug release matrix is Eudragit® RL-PO. In some embodiments, the drug release matrix is ethyl cellulose (EC). In some embodiments, the drug release matrix is hydroxypropyl methyl cellulose (HPMC) matrix.

[00112] In some embodiments, the HPMC matrix comprises between about 10 and about 50% HPMC. In some embodiments, the HPMC matrix comprises between about 5 and about 60% HPMC. In some embodiments, the HPMC matrix comprises between about 0 and about 60% HPMC. In some embodiments, the HPMC matrix comprises between about 10 and about 20% HPMC. In some embodiments, the HPMC matrix comprises between about 10 and about 15% HPMC. In some embodiments, the HPMC matrix comprises between about 10 and about 30% HPMC. In some embodiments, the HPMC matrix comprises between about 20 and about 40% HPMC. In some embodiments, the HPMC matrix comprises between about 20 and about 50% HPMC. In some embodiments, the HPMC matrix comprises between about 20 and about 60% HPMC. In some embodiments, the HPMC matrix comprises between about 40 and about 50% HPMC. In some embodiments, the HPMC matrix comprises between about 40 and about 60% HPMC. In some embodiments, the HPMC matrix comprises between about 50 and about 60% HPMC.

[00113] In some embodiments, the HPMC matrix comprises about 10% HPMC. In some embodiments, the HPMC matrix comprises about 15% HPMC. In some embodiments, the HPMC matrix comprises about 20% HPMC. In some embodiments, the HPMC matrix comprises about 30% HPMC. In some embodiments, the HPMC matrix comprises about 40% HPMC. In some embodiments, the HPMC matrix comprises about 50% HPMC. In some embodiments, the HPMC matrix comprises about 60% HPMC.

[00114] In some embodiments, the first and third layers form an exterior portion of the solid oral dosage form. In some embodiments, the solid oral dosage form disclosed herein, further comprising an excipient.

[00115] In some embodiments, the solid oral dosage form further comprises an agent selected from active pharmaceutical agents, cosmetic agents, nutraceutical agents, tablet compression aid, permeation enhancer, imaging agents, diagnostic agents, radioprotective agents, nutraceutical agents, enzymes, nutrient blockers, aptamers, antibodies, neutralizing agents, and combinations thereof. In some embodiments, the solid oral dosage form further comprises an enzyme. In some embodiments, the solid oral dosage form further comprises a nutrient blocker. In some embodiments, the solid oral dosage form further comprises a radioprotective agent. In some embodiments, the solid oral dosage form further comprises an active pharmaceutical agent. In some embodiments, the solid oral dosage form further comprises a diagnostic agent. In some embodiments, the solid oral dosage form further comprises a combination of two or more of enzymes, nutrient blockers, radioprotective agents, active pharmaceutical agents, and diagnostic agents. In some embodiments, the oral dosage form further comprises a permeation enhancer. In some embodiments, the second layer further comprises a permeation enhancer.

[00116] In some embodiments, the first and third layers further comprise a tablet compression aid. In some embodiments, the first layer further comprises a tablet compression aid. In some embodiments, the third layer further comprise a tablet compression aid. In some embodiments, the second layer further comprise a tablet compression aid. In certain embodiments, the tablet compression aid is a combination of lactose and cellulose. In certain embodiments, the tablet compression aid is a lactose. In certain embodiments, the tablet compression aid is a cellulose.

[00117] In some embodiments, the solid oral dosage form is in the form of a tablet. In some embodiments, the solid oral dosage form is in the form of a pill. In some embodiments, the solid oral dosage form is in the form of a capsule.

[00118] In some embodiments, the tablet is formed by a compression force of between 1 and 20 kN/m². In some embodiments, the tablet is formed by a compression force of between 2 and 10 kN/m².

[00119] In some embodiments, the second layer is encapsulated by the first layer. In some embodiments, the second layer is encapsulated by the third layer. In some embodiments, the second layer is encapsulated by the first and third layers. In some embodiments, at least a portion of the second layer forms an exterior surface of the solid oral dosage form. In some embodiments, the tablet is encapsulated by a fourth layer.

[00120] In some embodiments, the fourth layer is an enteric coating. In certain embodiments, the fourth layer aids in time-controlled release of the active pharmaceutical. In certain embodiments, the fourth layer aids in time-controlled release of the monomer. In certain embodiments, the fourth layer aids in time-controlled release of the oxygen source.

[00121] In some embodiments, the solid oral dosage form is stable in the stomach of the subject. In some embodiments, the solid oral dosage form is stable in the stomach for at least 30 minutes. In some embodiments, the solid oral dosage form is stable in the stomach for at least 60 minutes.

[00122] In some embodiments, the composition comprises a concentration of oxygen source compatible with ingestion by the subject.

[00123] In certain embodiments, the solid oral dosage form is administered orally, and the site of polymerization is within the GI tract.

[00124] In another aspect, this disclosure provides a method of administering an active pharmaceutical ingredient to a subject in need thereof, the method comprising administering to the subject the solid oral dosage form described herein.

[00125] In a further aspect, provided herein a method of reducing the dosing frequency of an active pharmaceutical ingredient in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form of the present disclosure.

[00126] In another aspect, provided herein a method of prolonging gastrointestinal retention of an active pharmaceutical ingredient in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form described herein. In some embodiments, the method is a method of prolonging the residence time of an active pharmaceutical agent at the site of polymerization in the subject as compared to the administration of the active pharmaceutical agent in the absence of the polymer.

[00127] In some embodiments, the method is a method of increasing the half-life of the active pharmaceutical agent as compared to the administration of the active pharmaceutical agent in the absence of the polymer. In some embodiments, the method increases the half-life of the active pharmaceutical agent by at least about 2-fold as compared to the administration of the active pharmaceutical agent in the absence of the polymer. In some embodiments, the method increases the half-life of the active pharmaceutical agent by at least about 4-fold as compared to the administration of the active pharmaceutical agent in the absence of the polymer. In some embodiments, the method increases the half-life of the active pharmaceutical agent by at least about 6-fold as compared to the administration of the active pharmaceutical agent in the absence of the polymer. In some embodiments, the method increases the half-life of the active pharmaceutical agent by at least about 10-fold as compared to the administration of the active pharmaceutical agent in the absence of the polymer.

[00128] In some embodiments, the method is a method of increasing the AUC of the active pharmaceutical agent as compared to the administration of the active pharmaceutical agent in the absence of the polymer. In some embodiments, the method increases the AUC by at least about 2-fold as compared to the administration of the active pharmaceutical agent in the absence of the polymer. In some embodiments, the method increases the AUC by at least about 3-fold as compared to the administration of the active pharmaceutical agent in the absence of the polymer. In some embodiments, the method increases the AUC by at least about 4-fold as compared to the administration of the active pharmaceutical agent in the absence of the polymer.

[00129] In some embodiments, the method is a method of modulating the C_{max} of the active pharmaceutical agent as compared to the administration of the active pharmaceutical agent in the absence of the polymer. In certain embodiments, the method of modulating is increasing. In certain embodiments, the method of modulating is decreasing.

[00130] In some embodiments, the method is a method of modulating the T_{max} of the active pharmaceutical agent as compared to the administration of the active pharmaceutical agent in the absence of the polymer. In certain embodiments, the method of modulating is increasing. In certain embodiments, the method of modulating is decreasing.

[00131] In some embodiments, the method does not affect drug metabolism once the active pharmaceutical agent is absorbed by the small intestine.

[00132] In one aspect, provided herein a method of sustaining the release of an active pharmaceutical ingredient in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form of the present disclosure. In some embodiments, the method is a method of providing for sustained release of an active pharmaceutical agent as compared to the administration of the active pharmaceutical agent in the absence of the polymer.

[00133] In one aspect, this disclosure provides a method of treating a bacterial infection in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form of the present disclosure.

[00134] In another aspect, provided herein a method of treating infectious disease in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form disclosed herein. In some embodiments, the disease is a bacterial infection. In some embodiments, the disease is a viral infection. In some embodiments, the infectious disease is a parasitic infection. In some embodiments, the infectious disease is a protozoological infection.

[00135] In one aspect of the present disclosure, is provided a method of treating a symptom of Parkinson's disease in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form described herein.

[00136] In another aspect, provided herein a method of increasing the half-life of an active pharmaceutical agent in the subject, the method comprising administering to the subject the solid oral dosage form of the present disclosure.

[00137] In a further aspect, this disclosure provides a method of increasing residence time of an active pharmaceutical agent in the subject, the method comprising administering to the subject the solid oral dosage form disclosed herein. In some embodiments, the method is a method of increasing residence time in the small intestine. In some embodiments, the method is a method of increasing residence time of one or more of nutrients and active pharmaceutical agents in the small intestine.

[00138] In one aspect, the solid oral dosage form disclosed herein or method provided herein, wherein the solid oral dosage forms a polymer *in vivo* in a subject following administration to the subject. In some embodiments, the method comprises administering to a subject a solid oral dosage form disclosed herein, wherein the oxygen source contacts an endogenous catalyst in a tissue of the subject and release of oxygen from the oxygen source polymerizes the monomer on the tissue.

[00139] In certain embodiments, the polymer forms in the digestive system. In some embodiments, the polymer forms on the gastrointestinal tract. In some embodiments, the polymer forms on the upper gastrointestinal tract. In some embodiments, the polymer forms on the small intestine. In some embodiments, polymer forms in the gut of the subject. In some embodiments, the polymer forms in the stomach of the subject. In some embodiments, the polymer forms in the esophagus of the subject. In some embodiments, the polymer adheres to a tissue of the subject. In certain embodiments, the polymer forms in contact with and adheres to a tissue in the subject.

[00140] In some embodiments, the location of polymer formation is based on expression levels of the catalyst. In certain embodiments, the polymer forms substantially on a particular tissue based on high expression levels of catalyst. In some embodiments, the polymer does not substantially form on a particular tissue due to low expression levels of catalyst. In some embodiments, the location of polymer formation is based on expression levels of catalase. In certain embodiments, the polymer forms substantially on a particular tissue based on expression levels of catalase. In some embodiments, the polymer does not substantially form on a particular tissue due to low expression levels of catalase.

[00141] In certain embodiments, the polymer forms in contact with and adheres to one or more of the dorsal portion of the tongue, buccal mucosa, labial mucosa, palate, nasal mucosa, trachea mucosa, small intestine, colon, ventral tongue, sclera, ileum, epidermis, bladder serosa, epicardium, liver surface, esophagus, duodenum, small intestine, peritoneum, stomach, small bowel, or intestinal epithelium. In some embodiments, the polymer binds with chemical moieties exposed on the surface of tissue in the digestive system. In some embodiments, the polymer binds with amine moieties exposed on the surface of tissue in the digestive system. In some embodiments, the polymer binds with thiol moieties exposed on the surface of tissue in the digestive system. In some embodiments, the polymer crosslinks with amine moieties exposed on the luminal surface of the epithelium of the subject. In some embodiments, the polymer crosslinks with thiol moieties exposed on the luminal surface of the epithelium of the subject.

[00142] In some embodiments, the polymer is rapidly formed. In some embodiments, the polymer is formed in less than about 20 minutes. In some embodiments, the polymer is formed in less than about 15 minutes. In some embodiments, the polymer is formed in less than about 12 minutes. In some embodiments, the polymer is formed in less than about 10 minutes.

[00143] In some embodiments, the endogenous catalyst is selected from catalases or peroxidases. In some embodiments, the endogenous catalyst is a peroxidase. In certain embodiments, the peroxidase is eosinophil peroxidase, lactoperoxidase, or myeloperoxidase. In some embodiments, the endogenous catalyst is a catalase. In some embodiments, the catalase is a bacterial catalase. In some embodiments, the catalase is a human catalase.

[00144] In certain embodiments, the endogenous catalyst is located in the digestive system. In some embodiments, the endogenous catalyst is located in the gastrointestinal (GI) tract of the subject. In some embodiments, the endogenous catalyst is located in the upper GI of the subject. In some embodiments, the endogenous catalyst is located in the gut of the subject. In some embodiments, the endogenous catalyst is located in the stomach of the subject.

[00145] In some embodiments, the polymer is in the form of a hydrogel. In some embodiments, the hydrogel has a concentration of alginate-dopamine (ALG-DA) of about 1-10%. In some embodiments, the hydrogel has a concentration of ALG-DA of about 4-15%. In some embodiments, the hydrogel has a concentration of ALG-DA of about 10-15%. In some embodiments, the hydrogel has a concentration of ALG-DA of about 15%. In some embodiments, the hydrogel has a concentration of ALG-DA of about 12%. In some embodiments, the hydrogel has a concentration of ALG-DA of about 10%. In some embodiments, the hydrogel has a concentration of ALG-DA of about 8%. In some embodiments, the hydrogel has a concentration of ALG-DA of about 6%. In some embodiments, the hydrogel has a concentration of ALG-DA of about 4%. In some embodiments, the hydrogel has a concentration of ALG-DA of about 2%. In some embodiments, the hydrogel has a concentration of ALG-DA of about 1%. In some embodiments, the hydrogel has a concentration of ALG-DA of less than 1%. In some embodiments, the hydrogel has a concentration of ALG-DA of less than 10%.

[00146] In some embodiments, the solid oral dosage form is nontoxic. In some embodiments, the solid oral dosage form and its components are nontoxic.

[00147] In another aspect, provided herein a kit comprising: a solid oral dosage form disclosed herein, and instructions for administering the solid oral dosage form to a subject.

Dosage forms, Kits, and Administration

[00148] In certain embodiments, the solid oral dosage form described herein provides an effective amount of the active pharmaceutical agent. In certain embodiments, the effective

amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the effective amount is an amount effective for treating a proliferative disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a proliferative disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating a hematological disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a hematological disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating a neurological disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a neurological disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating a painful condition in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a painful condition in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating a psychiatric disorder in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a psychiatric disorder in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating a metabolic disorder in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a metabolic disorder in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for reducing the risk of developing a disease (*e.g.*, proliferative disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof.

[00149] In certain embodiments, the subject is an animal. The animal may be of either sex and may be at any stage of development. In certain embodiments, the subject described herein is a human. In certain embodiments, the subject is a non-human animal. In certain embodiments, the subject is a mammal. In certain embodiments, the subject is a non-human mammal. In certain embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a companion animal, such as a dog or cat. In certain embodiments, the subject is a livestock animal, such as a cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a zoo animal. In another embodiment, the subject is a research animal, such as a rodent (*e.g.*, mouse, rat), dog, pig, or non-human primate. In certain embodiments, the animal is a genetically engineered animal.

In certain embodiments, the animal is a transgenic animal (*e.g.*, transgenic mice and transgenic pigs). In certain embodiments, the subject is a fish or reptile.

[00150] The disclosed solid oral dosage forms can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. A “unit dose” is a discrete amount of the solid oral dosage forms can comprise a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage, such as one-half or one-third of such a dosage.

[00151] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a solid oral dosage form described herein will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the dosage form is to be administered.

[00152] Pharmaceutically acceptable excipients used in the manufacture of provided solid oral dosage forms can include inert diluents or fillers, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the solid oral dosage forms.

[00153] Exemplary diluents or fillers include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, starches (such as dry starch, cornstarch), sugars (such as powdered sugar), calcium trisulfate, carboxymethylcellulose calcium, dextrate, dextrin, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium, maltitol, maltodextrin, maltose, sucrose, glucose, mannitol, silicic acid, xylitol, and mixtures thereof.

[00154] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose, and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl

cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

[00155] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (*e.g.*, acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.*, bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (*e.g.*, stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.*, carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.*, carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.*, polyoxyethylene sorbitan monolaurate (Tween[®] 20), polyoxyethylene sorbitan (Tween[®] 60), polyoxyethylene sorbitan monooleate (Tween[®] 80), sorbitan monopalmitate (Span[®] 40), sorbitan monostearate (Span[®] 60), sorbitan tristearate (Span[®] 65), glyceryl monooleate, sorbitan monooleate (Span[®] 80), polyoxyethylene esters (*e.g.*, polyoxyethylene monostearate (Myrij[®] 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol[®]), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.*, Cremophor[®]), polyoxyethylene ethers, (*e.g.*, polyoxyethylene lauryl ether (Brij[®] 30)), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic[®] F-68, poloxamer P-188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

[00156] Exemplary disintegrating agents or disintegrants include agar, algin, alginic acid, sodium alginate, silicates, sodium carbonate, calcium carbonate, carboxymethylcellulose, cellulose, clay, colloidal silicon dioxide, croscarmellose sodium, crospovidone, rubber, magnesium silicate, methylcellulose, potassium krillin, hydroxypropylcellulose (*e.g.*, low substituted Hydroxypropylcellulose), crosslinked polyvinylpyrrolidone, hydroxypropylcellulose, and starch (*e.g.*, sodium glycolate starch, potato or tapioca starch).

[00157] Exemplary binding agents include starch (*e.g.*, glycolate starch, cornstarch and starch paste), gelatin, sugars (*e.g.*, sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.*), natural and synthetic gums (*e.g.*, acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose,

methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinylpyrrolidone), magnesium aluminum silicate (Veegum[®]), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

[00158] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, antiprotozoan preservatives, alcohol preservatives, acidic preservatives, and other preservatives. In certain embodiments, the preservative is an antioxidant. In other embodiments, the preservative is a chelating agent.

[00159] Exemplary antioxidants include alpha tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[00160] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (*e.g.*, sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (*e.g.*, citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof.

[00161] Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[00162] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[00163] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[00164] Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[00165] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant[®] Plus, Phenonip[®], methylparaben, Germall[®] 115, Germaben[®] II, Neolone[®], Kathon[®], and Euxyl[®].

[00166] Exemplary buffering agents include citrate buffer solutions, tris buffer, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

[00167] Exemplary lubricating agents include agar, ethyl oleate, ethyl laurate, glycerin, glyceryl palmitostearate, magnesium oxide, magnesium stearate, mannitol, poloxamer, glycol, sodium stearyl, sorbitol, zinc stearate, magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behenate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[00168] Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mint, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride,

cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

[00169] Solid dosage forms for oral administration include tablets and pills. In such solid dosage forms, the active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, and (i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of tablets and pills, the dosage form may include a buffering agent.

[00170] The solid dosage forms of tablets and pills can be prepared with coatings and shells such as enteric coatings and other coatings well known in the art of pharmacology. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of encapsulating compositions which can be used include polymeric substances and waxes.

[00171] The active ingredient can be in a micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets and pills can be prepared with coatings and shells such as enteric coatings, release controlling coatings, and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active ingredient can be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such as a magnesium stearate and microcrystalline cellulose. In the case of tablets and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of encapsulating agents which can be used include polymeric substances and waxes.

[00172] Although the descriptions of the solid oral dosage form provided herein are principally directed to oral dosages which are suitable for administration to humans, it will be understood by the skilled artisan that such dosage forms are generally suitable for administration to animals of all sorts. Modification of solid oral dosage forms suitable for administration to humans in order to render the dosage forms suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[00173] Solid oral dosage forms provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the solid oral dosage forms described herein will be decided by a physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex, and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[00174] The solid oral dosage form provided herein can be administered enterally (*e.g.*, oral). The specifically contemplated route is oral administration.

[00175] The exact amount of the solid oral dosage form required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular active pharmaceutical agent, mode of administration, and the like. An effective amount may be included in a single dose (*e.g.*, single oral dose) or multiple doses (*e.g.*, multiple oral doses). In certain embodiments, when multiple doses are administered to a subject or applied to a tissue or cell, any two doses of the multiple doses include different or substantially the same amounts the dosage form described herein. In certain embodiments, when multiple doses are administered to a subject or applied to a tissue or cell, the frequency of administering the multiple doses to the subject or applying the multiple doses to the tissue or cell is three doses a day, two doses a day, one dose a day, one dose every other day, one dose every third day, one dose every week, one dose every two weeks, one dose every three weeks, or one dose every four weeks. In certain embodiments, the frequency of administering

the multiple doses to the subject or applying the multiple doses to the tissue or cell is one dose per day. In certain embodiments, the frequency of administering the multiple doses to the subject or applying the multiple doses to the tissue or cell is two doses per day. In certain embodiments, the frequency of administering the multiple doses to the subject or applying the multiple doses to the tissue or cell is three doses per day. In certain embodiments, when multiple doses are administered to a subject or applied to a tissue or cell, the duration between the first dose and last dose of the multiple doses is one day, two days, four days, one week, two weeks, three weeks, one month, two months, three months, four months, six months, nine months, one year, two years, three years, four years, five years, seven years, ten years, fifteen years, twenty years, or the lifetime of the subject, tissue, or cell. In certain embodiments, the duration between the first dose and last dose of the multiple doses is three months, six months, or one year. In certain embodiments, the duration between the first dose and last dose of the multiple doses is the lifetime of the subject, tissue, or cell. In certain embodiments, a dose (*e.g.*, a single dose, or any dose of multiple doses) described herein includes independently between 0.1 µg and 1 µg, between 0.001 mg and 0.01 mg, between 0.01 mg and 0.1 mg, between 0.1 mg and 1 mg, between 1 mg and 3 mg, between 3 mg and 10 mg, between 10 mg and 30 mg, between 30 mg and 100 mg, between 100 mg and 300 mg, between 300 mg and 1,000 mg, or between 1 g and 10 g, inclusive, of a solid oral dosage form described herein. In certain embodiments, a dose described herein includes independently between 1 mg and 3 mg, inclusive, of a solid oral dosage form described herein. In certain embodiments, a dose described herein includes independently between 3 mg and 10 mg, inclusive, of a solid oral dosage form described herein. In certain embodiments, a dose described herein includes independently between 10 mg and 30 mg, inclusive, of a solid oral dosage form described herein. In certain embodiments, a dose described herein includes independently between 30 mg and 100 mg, inclusive, of a solid oral dosage form described herein.

[00176] Dose ranges as described herein provide guidance for the administration of a provided solid oral dosage form to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[00177] A solid oral dosage form, as described herein, can be administered in combination with one or more additional pharmaceutical agents (*e.g.*, therapeutically and/or prophylactically active agents). The solid oral dosage form can be administered in

combination with additional pharmaceutical agents that improve their activity (*e.g.*, activity (*e.g.*, potency and/or efficacy) in treating a disease in a subject in need thereof, in preventing a disease in a subject in need thereof, in reducing the risk to develop a disease in a subject in need thereof, and/or in inhibiting the activity of a target, improve bioavailability, improve safety, reduce drug resistance, reduce and/or modify metabolism, inhibit excretion, and/or modify distribution in a subject or cell. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects. In certain embodiments, the solid oral dosage form described herein, including an additional pharmaceutical agent, shows a synergistic effect that is absent in the including one of the solid oral dosage forms and the additional pharmaceutical agent, but not both. In some embodiments, the additional pharmaceutical agent achieves a desired effect for the same disorder. In some embodiments, the additional pharmaceutical agent achieves different effects.

[00178] The solid oral dosage form can be administered concurrently with, prior to, or subsequent to one or more additional pharmaceutical agents, which may be useful as, *e.g.*, combination therapies. Pharmaceutical agents include therapeutically active agents. Pharmaceutical agents also include prophylactically active agents. Pharmaceutical agents include small organic molecules such as drug compounds (*e.g.*, compounds approved for human or veterinary use by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells. In certain embodiments, the additional pharmaceutical agent is a pharmaceutical agent useful for treating and/or preventing a disease (*e.g.*, proliferative disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder). Each additional pharmaceutical agent may be administered at a dose and/or on a time schedule determined for that pharmaceutical agent. The additional pharmaceutical agents may also be administered together with each other and/or with the solid oral dosage form described herein in a single dose or composition or administered separately in different doses or compositions. The particular combination to employ in a regimen will take into account compatibility of the solid oral dosage form described herein with the additional pharmaceutical agent(s) and/or the desired therapeutic

and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agent(s) in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[00179] The additional pharmaceutical agents include, but are not limited to, anti-proliferative agents, anti-cancer agents, anti-angiogenesis agents, steroidal or non-steroidal anti-inflammatory agents, immunosuppressants, anti-bacterial agents, anti-viral agents, cardiovascular agents, cholesterol-lowering agents, anti-diabetic agents, anti-allergic agents, contraceptive agents, pain-relieving agents, anesthetics, anti-coagulants, inhibitors of an enzyme, steroidal agents, steroidal or antihistamine, antigens, vaccines, antibodies, decongestant, sedatives, opioids, analgesics, anti-pyretics, hormones, and prostaglandins. In certain embodiments, the additional pharmaceutical agent is an anti-proliferative agent. In certain embodiments, the additional pharmaceutical agent is an anti-cancer agent. In certain embodiments, the additional pharmaceutical agent is an anti-viral agent. In certain embodiments, the additional pharmaceutical agent is an binder or inhibitor of a protein kinase. In certain embodiments, the additional pharmaceutical agent is selected from the group consisting of epigenetic or transcriptional modulators (*e.g.*, DNA methyltransferase inhibitors, histone deacetylase inhibitors (HDAC inhibitors), lysine methyltransferase inhibitors), antimetotic drugs (*e.g.*, taxanes and vinca alkaloids), hormone receptor modulators (*e.g.*, estrogen receptor modulators and androgen receptor modulators), cell signaling pathway inhibitors (*e.g.*, tyrosine protein kinase inhibitors), modulators of protein stability (*e.g.*, proteasome inhibitors), Hsp90 inhibitors, glucocorticoids, all-*trans* retinoic acids, and other agents that promote differentiation. In certain embodiments, the solid oral dosage form described herein can be administered in combination with an anti-cancer therapy including, but not limited to, surgery, radiation therapy, transplantation (*e.g.*, stem cell transplantation, bone marrow transplantation), immunotherapy, and chemotherapy. Additional pharmaceutical agents include small organic molecules such as drug compounds (*e.g.*, compounds approved by the US Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins and cells.

[00180] Also encompassed by the disclosure are kits (*e.g.*, pharmaceutical packs). The kits provided may comprise a solid oral dosage form described herein and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, the solid oral dosage form described herein provided in the first container and the second container are combined to form one unit dosage form.

[00181] Thus, in one aspect, provided are kits including a first container comprising a solid oral dosage form described herein. In certain embodiments, the kits are useful for treating a disease (*e.g.*, proliferative disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits are useful for preventing a disease (*e.g.*, proliferative disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits are useful for reducing the risk of developing a disease (*e.g.*, proliferative disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits are useful for inhibiting the activity (*e.g.*, aberrant activity, such as increased activity) of a target in a subject or cell.

[00182] In certain embodiments, a kit described herein further includes instructions for using the kit. A kit described herein may also include information as required by a regulatory agency such as the U.S. Food and Drug Administration (FDA). In certain embodiments, the information included in the kits is prescribing information. In certain embodiments, the kits and instructions provide for treating a disease (*e.g.*, proliferative disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits and instructions provide for preventing a disease (*e.g.*, proliferative disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits and instructions provide for reducing the risk of developing a disease (*e.g.*, proliferative disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits and instructions provide for inhibiting the activity (*e.g.*, aberrant activity, such as increased activity) of a target in a subject or cell. A kit described herein may include one or more additional pharmaceutical agents described herein as a separate composition.

EXAMPLES

Example 1: Design of an oral pill capable of prolonging intestinal residence

[00183] An oral dosage form with the ability to specifically adhere to the small intestine, sufficiently load various kinds of the therapeutic agents, provide controlled release of the agents, and show good biocompatibility was designed.^[39]

[00184] In order to load different drugs and not affect the adhesive property of the drug delivery system, a modular system was designed where a sustained release matrix of drug was located bound to either a single layer of mucoadhesive polymer, or between two layers of mucoadhesive polymer. A schematic depicting an embodiment of the modular sustained release drug delivery system disclosed herein and the strategy for dopamine-based *in situ* gelation and adhesion on intestine is shown in **FIGs. 1A-1C**. Most mucoadhesive polymers rely on weak non-specific interactions for adhering to the wall of the gastrointestinal tract. The inventors unexpectedly discovered that covalent interactions targeted to specific regions of the gastrointestinal tract leads to longer retention of pharmaceuticals and more reproducible results. To achieve this, a dopamine-conjugated alginate (ALG) polymer was used in the mucoadhesive layer. ALG has been widely applied as a drug carrier due to its biocompatibility, biodegradability, and relatively low cost.^[40, 41] Further, the mucoadhesive layer contained Tris base to provide buffering capacity and hydrogen peroxide as a source of oxygen. In the presence of intestinal catalase (CAT), hydrogen peroxide is converted to oxygen which leads to the oxidation of the dopamine side chains on ALG.^[42] This in turn leads to self-cross linking through Michael addition and Schiff base reaction to form hydrogel.^[43] The nanoparticles of polydopamine (PDA) from the formulation ingredients coordinate with ALG-DA hydrogel to enhance the cohesion of hydrogel. Oxidized ALG-DA covalently reacts with nucleophilic amine or thiol groups present in the tissue. The coordination and covalent bonds endow robust mucoadhesion in the hydrated intestinal environment.

Example 2: Alginate-dopamine preparation and characterization

[00185] The ALG-DA was synthesized by standard carbodiimide coupling chemistry (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride/N-hydroxysuccinimide (EDC/NHS) chemistry). In this reaction, the carboxyl group of ALG was activated by EDC/NHS and the amine group of dopamine was then coupled to the activated carboxyl group (**FIG. 2A**). The conjugation efficiency was determined by measuring absorbance at

280 nm using a UV–vis spectrophotometer. It was found that the conjugation of DA to polymer backbone depends on the molar ratio of ALG: DA. Specifically, the conjugation efficiency of DA to ALG backbone was 11.77 ± 2.64 % and 15.69 ± 1.43 % at ALG: DA molar ratios of 1:1 and 1:2, respectively. The conjugation of DA to ALG was confirmed by ^1H -nuclear magnetic resonance (^1H -NMR) based peaks of the catechol protons observed at around 7 ppm (**FIG. 2B**). UV-Vis analysis demonstrated there is characteristic absorption peak at about 270 nm for ALG-DA, which is the absorbance wavelength of DA (**FIG. 2C**). Similar conclusions were obtained by Fourier transform near infrared (FT-IR) analysis of the polymer. Characteristic absorptions of ALG (C-O-C at 1037 cm^{-1} , C-O at 1113 cm^{-1}) were identified in each group. The peaks at 1622 cm^{-1} and 1402 cm^{-1} were assigned to the N-H deformation and C-N stretching vibrations, respectively, which were remarkably strengthened after DA modification (**FIG. 2D**).

[00186] The rheological properties, micro-structure, and swelling behavior of hydrogels formed from ALG-DA were then characterized. To form hydrogels, the ALG-DA was mixed with free DA, hydrogen peroxide, Tris base, and CAT for the *in vitro* evaluation. Generation of oxygen from hydrogen peroxide promoted the oxidation of DA and cross-linking of the ALG-DA. The effect of ALG-DA concentration on the rheological behavior of ALG-DA hydrogels was investigated using a TA Instruments DHR-2 Rheometer. Oscillatory measurements indicate that both the storage modulus (G') and loss modulus (G'') of ALG-DA hydrogels increased with concentration. Oscillatory rheological properties were performed to determine the viscoelastic properties of the ALG-DA hydrogels. Samples were subjected to increasing frequency at a strain of 0.01% (**FIG. 2E**). The G' of the ALG-DA hydrogel was nearly consistent over the frequency range tested and was higher than the G'' at each frequency in the 2% and 4 % ALG-DA hydrogel. The G' values for the hydrogel were initially independent of oscillation frequency across different concentrations and G' was greater than the G'' , indicating that these hydrogels were chemically crosslinked and that cross-linking in the ALG-DA hydrogel was highly stable and uniform. Higher G' for hydrogels of higher concentrations likely resulted from a higher degree of crosslinking. Elevated G'' values indicated strong viscous dissipation properties resulting from the breaking of the hydrogel. At strains around 1, the G' values of hydrogels decreased rapidly with the increase of strain, suggesting the gels underwent gel-sol transition and behaved as liquids. The cross point of G' and G'' , representing the transition of the gel network to a liquid state (solution behavior: $G' < G''$, solid behavior: $G' > G''$) (**FIG. 2E**). Time sweep

data show that the G' and G'' values of ALG-DA hydrogels separately increased from ~ 10 and ~ 100 Pa to ~ 20 and ~ 200 Pa with ALG-DA concentration from 2% to 4 % (**FIG. 2E**). The precursor solution of ALG-DA formed hydrogel within 30 minutes of gelation (**FIG. 2F**). Scanning electron microscope (SEM) analysis demonstrated that ALG-DA hydrogel has a well-defined lamellar structure with interconnected pores. The high concentration of ALG-DA hydrogel (4 % W/V) produced smaller and more porous specimens than the low concentration of ALG-DA hydrogel (2 % W/V) due to increasing of viscosity of the hydrogel solution which prevented the bubbles from escaping from the solution and supported interconnected channels. The relative higher cross-linking agent concentration in low concentration hydrogels resulted in an increase in entanglement between monomer and polymer which resulted in decreased porosity (**FIG. 2G**).

[00187] The swelling properties of ALG-DA hydrogel were examined by measuring the change in hydrogel weight during incubation under intestinal physiological conditions (in a PBS solution at 37 °C) (**FIG. 7**). The swelling ratios of the ALG-DA hydrogels were $192.9 \pm 14.5\%$ for 2% (W/V) ALG-DA and $229.7 \pm 3.8\%$ for 4% (W/V) ALG-DA. The porosity and gel fraction increased with increase in ALG-DA content, which allowed more water to enter the films and support swelling. The swelling behavior of the hydrogel gave an insight into its well-crosslinked network.

[00188] This example demonstrated that catechol-functionalized alginate polymers inspired by mussel adhesive chemistry generated highly organized and controllable hydrogels.

Example 3: Gelation in vitro and in vivo

[00189] It was investigated whether ALG-DA hydrogels spiked with DA could cross-link via polymerization on the surface of the gastrointestinal tract. Additionally, the degree of polymerization across the different portions of the gastrointestinal tract was investigated [44, 45].

[00190] The PDA embeds into the ALG-DA hydrogel network to strengthen the mechanical strength of hydrogel [46]. The polymerization of dopamine in the hydrogel system was shown in **FIGs. 8A-8B**. After centrifugation to measure the diameter of PDA by dynamic laser scattering (DLS) (Zetasizer Nano ZS90 instrument, Malvern Panalytical), the size of PDA was 469.5 ± 12.20 nm for 0.5 % (w/v), 402.26 ± 68.88 nm for 1 % (w/v) and 1189.33 ± 54.12 nm for 2% (w/v). When 1% DA was used in the formulations, hydrogels were formed within 20 minutes. The lower and higher concentration of DA influenced the gel formation speed. The

lower concentration of DA formed nanoparticles too slowly, while the higher concentration of DA formed much larger aggregates along with a small amount of the desired nanoparticles, which could not efficiently link the polymer together. During the oxidation process of DA, some amount of PDA covalently couples on the surface of ALG-DA matrix, which also contributed to the properties of the hydrogel. The lower concentration of DA cannot interact with the DA on the ALG-DA networks, which leads to the slow gelling. PDA is a heterogeneous material in which an unpolymerized self-assembled structure is included during oxidative polymerization of DA^[47]. The higher concentration of DA forming PDA with large size, which is more likely to be a supramolecular aggregate, held together primarily through noncovalent interactions, and did not form long-chain networks^[48].

[00191] Pills made from ALG-DA, dopamine, hydrogen peroxide, and Tris were placed on the surface of various segments of the porcine GI tract. After cross-linking, the hydrogel was observed to have a brown color due to the oxidation of the catechol moiety followed by polymerization, which is also a sign of gelation (**FIGs. 3A-3B**). This allowed investigation of the degree of polymerization using colorimetric analysis. The process of hydrogel formation on different porcine GI tissues were recorded using digital camera (**FIG. 3C**) and darkness measurements using image J software (**FIG. 3D**). Gels were formed faster on the small intestine compared to the esophagus and stomach, which indicated the potential to target the pills to adhere to the lower GI tract. When hydrogel-containing pills were delivered to the small intestine, mucoadhesive hydrogel was observed within 10 minutes (**FIG. 3E**).

[00192] In sum, this example showed that ALG-DA rapidly polymerized on the surface of the small intestine.

Example 4: Adhesion and erosion assay in vitro

[00193] To investigate the adhesion of the pills to the surface of the intestine, an adjustable tilted fixture was developed. The setup allowed up to 4 flow paths with adjustable angles (15, 30, 45 degree); flow can be diverted to adjust volumetric flow through each individual nozzle (**FIG. 4A**). Tablets made from alginate, alginate cross-linked with calcium, or ALG-DA hydrogels were placed on top of the tissue. Following 10 minutes of incubation time, water was flowed, and retention of the pills was measured. ALG-DA pills were retained on the intestine for a longer period in comparison to ALG-Ca pills (**FIG. 4B**). Further, the retention time of 30 pills on small intestinal tissue mounted on the flow table was examined. ALG-Ca pills became dislodged after a few seconds (at ≈ 5 seconds), the ALG-DA pills remained

adherent to the small intestine for more than 10 minutes, at which time the measurement was stopped (**FIG. 4C**).

[00194] The size of the pills was measured with a caliper at predetermined time intervals during the water flushing assay. ALG pills were used as controls, and graphite was added to the ALG pills to investigate the erosion process (dark color) (**FIG. 4D**). With the increase of water flushing time from 0 to 30 minutes, the sizes of ALG-DA pills increased 1.2 times due to the forming of hydrogels. The sizes of ALG pills decreased due to ALG dissolved and eroded from pills. After 30 minutes of flushing, ALG pills were eroded completely, while ALG-DA pills remained in place (**FIG. 4E**). These results further confirmed that the ALG-DA pills showed the significantly longer duration than ALG pills.

Example 5: In vitro release

[00195] The middle-layer of pills was fabricated with hydroxypropyl methyl cellulose (HPMC) and loaded with a hydrophobic drug combination (levodopa and carbidopa) or a hydrophilic drug (amoxicillin) (**FIG. 5A**). HPMC was selected as a drug release matrix because of its hydrophilic nature and capacity to produce sustained drug release. Various drug formulations were prepared by mixing drugs and HPMC in different ratios (**Figs 9A-9B**).

[00196] Drug-HPMC pills were assembled for the hydrophilic antibiotic amoxicillin, which is used for the treatment of pediatric pneumonia, and for the hydrophobic levodopa/carbidopa combination, an anti-Parkinson's disease drug combination was used. As compared with the control group (lactose pills), the drug release rate from the HPMC matrix was sustained for amoxicillin, levodopa, and carbidopa. Furthermore, the HPMC formulations (test group) showed a linear kinetic profile with limited burst release of amoxicillin and levodopa/carbidopa (**FIG. 5A**).

[00197] The influence of HPMC percentage on drugs' release profiles was investigated. Drug release from pills was assessed in PBS for amoxicillin and PBS containing 2% sodium dodecyl sulfate for the levodopa/carbidopa (**figs 9A-9B**). A range of HPMC matrices were assayed for drug release: one containing 10% HPMC (low viscosity), one containing 20% HPMC (low viscosity), the third containing 50% HPMC (high viscosity). The rate of release of amoxicillin from 50% HPMC (high viscosity) was slower than other three matrices, and all formulations showed a linear release kinetic profile. For levodopa/carbidopa, the release from

pills with 20% HPMC (low viscosity) showed more sustained and linear profile than 10 % HPMC (low viscosity).

[00198] Those skilled in the art will appreciate that the ratio of drug to HPMC can be tuned to provide controlled release based on the hydrophobic or hydrophilic characteristics of the drug.

Example 6: In vivo retention evaluation

[00199] A swine model was used for investigating the intestinal residence and the drugs' PK, as the anatomy of the pig intestine closely resembles that of humans', and pigs used in this study had a body weight comparable to adult humans. The intestinal residence of the dosage forms was accordingly characterized in female Yorkshire pigs (50 to 80 kg) from Tufts University (Grafton, MA) using periodic radiographs. Small intestinal residence was evaluated by periodic radiographic evaluation. Under anesthesia, pills were introduced using an over tube and endoscope into the small intestine. Representative serial abdominal radiographs after administration revealed that the ALG-DA triple-layer pills remained in the intestinal tract for over 24 hours. For the control pills (lactose pills), there were no radiographic signals at 6 hours (**FIG. 5B**).

[00200] Without wishing to be bound by theory, the inventors posit that a triple layer solid oral dosage form may be advantageous as this modality provides additional opportunities for the monomer-containing layer to contact the target tissue (e.g., intestinal epithelial layer), thus initiating polymerization regardless of which surface portion of the dosage form initially contacts the target tissue, preventing the dosage form from being flushed away.

Example 7: Pharmacokinetics in a large animal model

[00201] The ALG-DA triple-layer pills containing amoxicillin in the middle layer were administered (ALG-DA pills, test group) in the intestine of female Yorkshire pigs (50 to 80 kg) from Tufts University (Grafton, MA) under anesthesia. Pills containing amoxicillin with lactose were used as the control (Control pills, control group). The pharmacokinetic parameters (including half-life ($t_{1/2}$), mean retention time (MRT), maximum concentration (C_{max}), peak time (T_{max}), and area under the curve (AUC)) of drugs in pigs were calculated using a noncompartment pharmacokinetics model. Results demonstrated that a 11.5-fold increase between the $t_{1/2}$ of amoxicillin test group and control group. T_{max} increased by 1.5-fold (from 3.3 to 5.0 hours), MRT increased by 2.9-fold (from 4.3 to 12.3 hours) ($p < 0.05$,

compared with control group, Independent Samples T-Test, SPSS), which demonstrated that the developed universal pill formulations using the GSEL technology prolonged intestinal residence of hydrophilic drug-amoxicillin. There was no significant difference between the AUC of amoxicillin test group and control group ($p>0.05$, compared with control group, Independent Samples T-Test, SPSS) (**FIGs. 6A-6B**). The PK parameters are shown in Table 1.

[00202] The pharmacokinetics (PK) of the levodopa-carbidopa administered as immediate-release formulations were then analyzed. Control pills with lactose containing both levodopa and carbidopa, control group and the ALG-DA triple-layer pills (ALG-DA pills containing both levodopa and carbidopa, test group) were used. Results demonstrated a 5-fold increase between the $t_{1/2}$ of levodopa test group and control group. T_{max} increased by 1.7-fold (from 3.3 to 5.7 hours), MRT increased by 2.3-fold (from 4.7 to 11 hours) ($p<0.05$, compared with control group, Independent Samples T-Test, SPSS), which demonstrated that the developed triple-layered pill formulation using the GSEL technology prolonged intestinal residence of hydrophobic drug-levodopa. A prolonged half-life can result in sustained clinical benefit. AUC of levodopa in the test group increased 2.2-fold compared with control group ($p<0.05$, compared with control group, Independent Samples T-Test, SPSS) (**FIGs. 6C-6D**). C_{max} after a single-dose administration of ALG-DA pills decreased. Reduced peak plasma concentration may decrease the symptoms of high concentration (peak level), such as hand tapping and walking time ^[52]. The PK parameters are shown in Table 1.

[00203] Levodopa and carbidopa are hydrophobic drugs and have good intestinal permeation. Through increasing the T_{max} or MRT using the developed system, the AUC_{0-t} was improved. This example shows that the development of mucoadhesive triple-layer pills enabled both hydrophilic and hydrophobic drugs' oral sustained delivery. The disclosed dosage forms can load a range of drugs with high doses, while avoiding interference with the mussel inspired adhesive's mechanical and gelling properties, which prolongs the $t_{1/2}$ of drugs and reduces the dose frequency.

Table 1 Parameters of drugs pharmacokinetics in pigs' plasma

PK Parameters	Amoxicillin		Levodopa	
	Control group	Test group	Control group	Test group
$t_{1/2}$ (h)	1.33 $\pm$ 0.56	15.28 $\pm$ 14.85*	1.19 $\pm$ 0.65	5.95 $\pm$ 1.52*
T_{max} (h)	3.33 $\pm$ 0.58	5 $\pm$ 0*	3.33 $\pm$ 0.58	5.67 $\pm$ 2.08*
C_{max} (ng/mL)	2905.13 $\pm$ 546.33	1573.6 $\pm$ 638.64*	14495.33 $\pm$ 9244.42	9633.3 $\pm$ 3734.54*
MRT (h)	4.3 $\pm$ 0.26	12.33 $\pm$ 5.5*	4.76 $\pm$ 0.72	10.98 $\pm$ 2.46*
AUC (ng/mL*h)	7732.25 $\pm$ 2418.25	7092.57 $\pm$ 1209.64	37878.32 $\pm$ 11330.11	84626.71 $\pm$ 60445.21*

*P<0.05, compared with control group, which demonstrates that differences are statistically significant, Independent sample T-test.

Example 8: Safety evaluation in vitro, ex vivo and in vivo

[00204] The biocompatibility of the ALG-DA hydrogels in *in vitro* and *in vivo* was evaluated.

[00205] The safety of the material was assessed by testing its cytotoxicity *in vitro* ^[54].

HEK293T cells, Caco-2 cells, Hs888Lu cells, HT29 cells and HepG2-C3A cells were used to assess cytotoxicity of ALG-DA hydrogel. The cells were treated with extracts of ALG-DA hydrogel and cell viability was measured using 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) test. The relative cell viabilities were all above 80% for all groups after 6 hours and 24 hours incubation (**FIGs. 10A-10B**).

[00206] For *in vivo* safety evaluation in rats, 2 groups of rats were used with 5 rats in each group. One group was administered water (control group). Another group was administered ALG-DA based pills powder, including ALG-DA, DA, H₂O₂, Tris (test group). The rats were gavaged every day for 1 month and weighed every day (**FIG. 11**). There were no changes in behavior and no treatment-related morbidity or mortality was observed. Very mild weight loss was observed which is likely due to the barrier function from the combined ALG-DA system.. The blood was taken for biochemical analysis (**FIG. 13**) and complete blood counts (**FIG. 14**), which demonstrated that there was no abnormality compared with the reference ranges. The brain, heart, liver, spleen, lung, and kidney were then harvested to perform histological analysis. The results are shown in **FIGs. 12A-12I**, which demonstrated that there were no adverse reactions.

[00207] Local toxicity of the ALG-DA pills was analyzed in swine tissue *ex vivo*. Pills were fixed on the small intestine of pigs, and after 6 hours, the tissue attached to the pills was harvested and processed for histology. Small intestinal mucosal surfaces did not show any injuries (**FIG. 12J**).

Experimental

[00208] *Materials*: Alginic acid sodium salt from brown algae, Dopamine hydrochloride, barium sulfate, dimethylsulfoxide, Trizma base, Phosphate-buffered saline (PBS, pH 7.4), Hydrogen Peroxide, (Hydroxypropyl)methyl cellulose were available commercially from Sigma-Aldrich. EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), N-Hydroxysuccinimide, BupH™ MES Buffered Saline, Sodium Dodecyl Sulfate (SDS), Deuterium oxide, Hydrochloric Acid Solution, Graphite (ACROS Organics™), Levodopa (USP, 98-102%, Spectrum™), Carbidopa (USP, 98-102%, Spectrum), L-(-)- α -Methyldopa (hydrate) (98%), Phosphate-Citrate Buffer pH5.5), Vybrant™ MTT Cell Viability Assay, Hydroxypropyl methylcellulose were purchased from Fisher scientific. Nanopure water (18M Ω cm) was acquired by means of a Milli-Q water filtration system, Millipore (St. Charles).

[00209] *Synthesis of Alginate-Dopamine*: Alginate modified with dopamine was synthesized using EDC-NHS chemistry. In brief, alginate (500 mg) was dissolved in MES (PH 4.7, 50 mL) solution. The solution was mixed with EDC and NHS at a 1:2:2 molar ratio of alginate monomer, EDC and NHS and reacted for 1 hour. Then dopamine was added into the reaction solution at a 2:1 or 1:1 molar ratio to alginate monomer and reacted for over 12 hours. The pH was maintained at 5.0. The reaction mixture was dialyzed using PBS (Adjusting pH 5.5 using 1N hydrochloric acid solution) and distilled water (Adjusting pH 5.5 using 1N hydrochloric acid solution) for 12 hours. The resulting conjugate was lyophilized for 5 days and then stored at -20°C.

[00210] *Ultraviolet–Visible Spectrophotometry*: Ultraviolet–visible spectrophotometer (Bruker, Billerica, MA, USA) was used to confirm the introduction of dopamine on the alginate backbone. A solution of ALG-DA (1 mg·mL⁻¹) in phosphate-citrate buffer at pH 5.5 was prepared and placed in 1 cm quartz cells. The wavelength used for this analysis was 280 nm. Phosphate-citrate Buffer (pH 5.5) was used as the reference solution.

[00211] *Nuclear Magnetic Resonance*: ¹H-NMR analyses were carried out by dissolving the alginate, dopamine, and alginate-dopamine in deuterated water (D₂O). The concentration is 1

mg·mL⁻¹. The spectra were obtained using a spectrometer Bio Spin 400 MHz (Bruker, Billerica, MA, USA). The spectra were recorded at 298 K and 400 MHz for 1H.

[00212] *Infrared spectroscopy*: Infrared spectra were recorded on a FTIR6700 Fourier Transform Infrared Spectrometer (Bruker, Billerica, MA, USA) and analyzed using OPUS v. 6,5,92 software.

[00213] *Scanning electron microscope*: Surface morphology of the dehydrated alginate-dopamine hydrogels were observed using the scanning electron microscope FlexSEM 1000 II. 2% (W/V) and 4% (W/V) hydrogels were lyophilized and fixed to aluminum stubs with double-sided adhesive carbon conductive tape and subsequently sputter coated with carbon using a SC 7620 mini sputter coater, then scanned at 5.0 kV voltages and 50 Pa vacuum conditions with ultra-variable-pressure detector (UVD), respectively.

[00214] *Rheological properties test*: Rheological properties of the ALG-DA hydrogels were characterized using a TA Instruments DHR-2 Rheometer. ALG-DA dissolved in PBS (at 2% and 4% (w/v) concentration) was mixed with tris, H₂O₂, and catalase to initiate cross-linking of ALG-DA. The moduli of the hydrogels were measured using an angular frequency (0.1–100 rad/s at 1% strain) sweep. Hydrogel discs (diameter=8 mm, n=3) were assessed in parallel plates at a loading gap distance that was set at 5000 µm that of the individual hydrogel thickness, as measured by a digital caliper.

[00215] *Swelling of alginate-dopamine*: The swelling of ALG-DA hydrogels was measured by incubating the samples in PBS at 37 °C on a shaker at 100 r.p.m and subsequently measuring the weights at predetermined time intervals, then comparing with their initial weights.

[00216] *Gelation in vitro and in vivo*: All tissue and *in vivo* animal assays were performed in accordance with the approval of the MIT Committee on Animal Care. The bio-adhesive layers of triple-layer pills were prepared and their gelation was characterized *in vitro* and *in vivo*. The covalent reaction of dopamine-based polymer changed color, the hydrogel becomes dark, which is also the sign of gelation. Pills' gelation was characterized on different portions of porcine GI tract (esophagus, stomach, small intestine, colon) at different time-points. Pictures were taken of the pills and their darkness was calculated via image J software to analyze the gelation degree. ImageJ/FIJI - measure tool was used to quantify the color change of the pill over time. Images were converted to grayscale before processing. For processing, a rectangular contour of 1 mm² was used as a selection mask to repeatedly measure the intensity using Analyze tool. Each pill signal intensity was determined by the relative

intensity ratio compared to the small intestine as a background. Five measurements were taken for each pill across the pill area. The equation used was: Darkness ratio (%) = (Brightness intensity value of the small intestine - brightness intensity value of the pill) / Brightness intensity value of the small intestine × 100%. The pills were delivered to the intestine of pigs through an overtube, and then pictures were taken to investigate the gelation of pills on the small intestine of pigs *in vivo*.

[00217] *Adhesion assessment in vitro*: Adhesion studies were performed by employing a designed setup (**FIG. 4A**). Excised porcine intestinal tissues were cut and opened to line the slide of the apparatus. With the detachable slide from the apparatus laid flat, alginate-calcium pills (ALG-Ca) and alginate-dopamine pills (ALG-DA) were placed on the tissue at a shape of MIT. They were incubated at room temperature for 10 minutes, allowing the pills to get wet. The slide was turned upside down to ensure that the devices had adhered and was returned to the apparatus at a tilt angle of 45°. At room temperature, the fixed mucosal intestinal tissue was continuously flushed with water. The times for dislodgment were documented and compared for the different formulations. Videos were recorded with a digital camera and sequential photographs from the video recordings were collected. Oxidation products of ALG-DA pills (ALG-PDA) and ALG-DA pills were placed on the tissue. The tissue was continuously flushed with water. Video and pictures were recorded with a digital camera at predetermined time intervals.

[00218] *Erosion assay in vitro*: The erosion of alginate-dopamine pills (ALG-DA) was measured by placing them on the tissue, using alginate pills (ALG) as a control. The apparatus was set at a tilt angle of 45°. At room temperature, the fixed mucosal intestinal tissue was continuously flushed with water. Pictures of pills were recorded with a digital camera and the sizes of pills were measured by a caliper at predetermined time intervals. Four replicates were conducted for each sample.

[00219] *In vitro drug release*: The pill was submerged in PBS (50 mL) in a VWR (50 mL) centrifuge tube. Three replicates were used for each time point, and conditions were incubation at 37 °C on a shaker plate at 100 r.p.m. At each time point, release medium (1 mL) was replaced by fresh medium (1 mL) and then kept in refrigerator until analysis. Data collection was carried out for 24 hours, and the total drug release was measured by HPLC.

[00220] *In vivo residence test*: All animal studies were approved by the Committee on Animal Care at the Massachusetts Institute of Technology (CAC Protocol Number: 0919-058-22). To assess pills' retention in small intestine cavity, radiopaque barium sulfate-labeled

pills were administered via the overtube into the small intestine of female Yorkshire pigs (50 to 80 kg) from Tuft University (Grafton, MA). Pigs were anesthetized with an intramuscular injection of Telazol (5mg/kg), xylazine (2mg/kg), and atropine (0.04mg/kg). They were incubated and maintained on isoflurane gas anesthesia. Pills were introduced using an overtube and endoscope into the small intestine. Radiographs were performed at different time-points to monitor the transit of the pills.

[00221] *Oral pharmacokinetics studies:* All procedures were conducted in accordance with protocols approved by the Committee on Animal Care at the Massachusetts Institute of Technology (CAC Protocol Number:0919-058-22). The pharmacokinetics (PK) of amoxicillin and levodopa/carbidopa administered as a standard-release pill were compared. Control pill (Amoxicillin, 8 mg of drug per Kg pig, Levodopa, 10 mg of drug per Kg pig, Carbidopa, 2.5 mg of drug per Kg pig) or an ALG-DA triple-layer pill (ALG-DA pill, Amoxicillin, 20 mg of drug per Kg pig, Levodopa, 10 mg of drug per Kg pig, Carbidopa, 2.5 mg of drug per Kg pig) were used in female Yorkshire pigs (50 to 80 kg) from Tuft University (Grafton, MA). Pigs were fed daily in the morning and in the evening, with a diet of pellets (Laboratory Mini-Pig Growler Diet, 5081), with a midday snack of various fruits and vegetables. Pigs were on liquid diet for 24 hours before the procedure and fasted overnight. Pigs were sedated with intramuscular injection of midazolam (0.25mg/kg) with dexmedetomidine (0.03mg/kg) (survival studies). For longer hour study or terminal days, pigs were anesthetized with an intramuscular injection of Telazol (5mg/kg), xylazine (2mg/kg), and atropine (0.04mg/kg). They were incubated and maintained on isoflurane gas anesthesia. An overtube was placed with endoscopic guidance into the proximal intestine. The pills were placed into the intestine via the overtube, one dosage form per animal. After treatment administration, the overtube was carefully removed. At various times, blood was drawn from the mammary vein and transferred to a BD Vacutainer serum separator tubes (Becton, Dickinson and Co.). The tubes were centrifuged (3202g, 10 minutes, 4 °C), and the serum was collected and stored at -80 °C until further analysis. The samples were analyzed by liquid chromatography–tandem mass spectroscopy (LC-MS/MS) for serum amoxicillin and levodopa concentration.

[00222] *Cytotoxicity assay:* The alginate-dopamine hydrogel was incubated in the culture medium with a range of dosage from 0.2 to 2 mg·mL⁻¹ at 37 °C for 6 hours or 24 hours. The obtained medium was then tested for its toxicity toward cells. Cell lines were purchased from ATCC. Cytotoxicity was analyzed for HEK293T cells, Caco-2 cells, Hs888Lu cells, HT29

cells and HepG2-C3A cells by seeding them each in a 96-well plate at a density of 10,000 cells per well. Cells were kept in culture for 24 hours before replacing the medium with the pre-prepared solutions (100 μ L) as described above. After 6 hour or 24 hour culture, these solutions were replaced with untreated media (100 μ L) and cytotoxicity was quantified by adding MTT reagent (10 μ L) to each well. The contents were mixed and then allowed to be incubated at 37 °C for 4 hours. Absorbance wavelength was recorded on an Infinite® M200Pro (Tecan) with excitation at 540 nm. Cells that were not subjected to hydrogel-treated media provided a control. Before and after treated with hydrogel, pictures of the cells lines were taken to investigate their status. Cell viability was calculated by the following equation: cell viability (%) =

$$\frac{[\text{Absorbance}(\text{sample}) - \text{Absorbance}(\text{blank})]}{[\text{Absorbance}(\text{control}) - \text{Absorbance}(\text{blank})]} \times 100\%$$

[00223] *In vivo safety evaluation:* All animal procedures were conducted in accordance with protocols approved by the Committee on Animal Care at the Massachusetts Institute of Technology (CAC Protocol Number:0919-058-22). In order to analyze *in vivo* toxicity of the polymers, the minimum of 5 rats (Sprague Dawley, Male, 250g, Charles River, MA, USA) were dosed for each of groups. Pills were first pulverized to allow administration via oral gavage. This powder was weighed and re-suspended in sufficient water to obtain an ingestible suspension with the highest amount of material. The alginate-dopamine was administered daily. The maximum dose is 60 mg/kg rats. Suspensions (10 mL/kg body weight) were gavaged orally. Control rats were administered water (10 mL/kg). The weight, behavioral changes, and overall health of the rats were monitored daily for 28 days. After 28 days, animals were euthanized by CO₂ asphyxiation and necropsied. Blood of each rat was harvested in serum separator tubes and spun down. The serum was aliquoted in a screw cap tube and frozen at -20°C until further chemistry indexes analysis. Whole blood was used for complete blood counts test. Brain, heart, liver, spleen, lungs, kidney, stomach, small intestine, large intestine were extracted, weighed, and sectioned for histopathological examination. An independent pathologist examined all organs to detect any abnormalities in a blinded fashion.

[00224] *Statistical analyses:* The measurements are presented as means $\pm$ SD. Data were analyzed by independent sample T-test analysis of variance using SPSS. Between-groups differences were considered significant when *P* was < 0.05.

[00225] *High performance liquid chromatography.* High Performance Liquid Chromatography (HPLC) was used to determine the drug concentrations from all *in vitro*

release assays. An Agilent 1260 Infinity II HPLC system equipped with a quaternary pump, autosampler, thermostat, control module, and diode array detector was used. Data processing and analysis was performed using OpenLab CDS ChemStation®.

[00226] Levodopa and Carbidopa were separated on an Agilent Zorbax Eclipse XDB C18 analytical column 4.6 x 150 mm with 5 µm particles, maintained at 30 °C, using the optimized mobile phases A: 10 mM sodium phosphate buffer at pH 3.00, and B: acetonitrile. Isocratic elution was employed over a 6-minute period to separate both compounds using a mobile phase composition of 90% A and 10% B. The injection volume was 5 µL, and the selected ultraviolet (UV) detection wavelength was 254 nm at a bandwidth of 4.0, no reference wavelength, and an acquisition rate of 10 Hz.

[00227] Amoxicillin was separated on a Phenomenex Kinetex PS C18 analytical column 4.6 x 150 mm with 2.6 µm particles, maintained at 30 °C using the optimized mobile phases A: 10 mM ammonium acetate at pH 4.00, and B: methanol. Isocratic elution was employed over a 5-minute period to separate both compounds using a mobile phase composition of 30% A and 70% B. The injection volume was 5 µL, and the selected ultraviolet (UV) detection wavelength was 230 nm at a bandwidth of 4.0, no reference wavelength, and an acquisition rate of 10 Hz.

[00228] *Liquid chromatography tandem-mass spectrometry.* Samples containing levodopa and carbidopa in swine serum from *in vivo* assays were prepared by protein precipitation and a simple derivatization protocol adapted from the method presented by Junnotula and Licea-Perez.^[59] Stock solutions of each compound were prepared in methanol at a concentration of 500 µg/mL containing H₃PO₄ (1%v/v). A twelve-point calibration curve was prepared in black swine serum ranging from 10-25000 ng/mL. 100 µL of each sample was spiked with 50 µL of 500 ng/mL levodopa-d₃ in acetonitrile as internal standards for levodopa. Then 400 µL of fluorecamine at 5mg/mL in acetonitrile was added to each sample. Samples were centrifuged for 10 minutes at 13,000 rpm. 300 µL was pipetted into fresh Eppendorf tubes and allowed to incubate covered at 37 °C for 60 minutes. Following incubation, 200 µL of supernatant was pipetted into a 96-well plate containing 200 µL of water. Analyte concentrations of levodopa and deuterated internal standard were analyzed using Ultra-Performance Liquid Chromatography-Tandem Mass Spectrometry (UPLC-MS/MS). Analysis was performed on a Waters ACQUITY UPLC®-I-Class System aligned with a Waters Xevo® TQ-S mass spectrometer (Waters Corporation, Milford MA). Liquid chromatographic separation was performed on either an Acquity UPLC® CSH (50mm ×

2.1mm, 1.7 μ m particle size) column at 50 °C. Sample introduction and ionization were performed by electrospray ionization (ESI) in the positive ionization mode. 10.0 μ L was injected onto the instrument for analysis. For the analysis of levodopa and deuterated internal standards, the following mobile phase was used: A (aqueous): 0.1% formic acid, 10mM ammonium formate solution and B (acetonitrile): 10 mM ammonium formate, 0.1% formic acid solution (95:5 v/v). The mobile phase had a continuous flow rate of 0.45 mL/min for using a time and solvent gradient composition. The initial composition, 95% Mobile Phase A, was held for 1.00 minutes. Following which, the composition was changed linearly to 5% Mobile Phase A and 95% Mobile Phase B until 1.25 minutes. The composition was held constant at 95% Mobile Phase B until 3.00 minutes. At 3.25 minutes the composition returned to 95% Mobile Phase A, where it remained for column equilibration for the duration of the run, ending at 4.00 minutes. Waters MassLynx 4.1 software was used for data acquisition and analysis. The mass to charge transition (m/z) used to quantitate levodopa fluorecamine was 458.16>139.137 and 461.16>232.4 for levodopa-d3 fluorecamine.

[00229] *Swine serum sample preparation.* Samples containing amoxicillin in swine serum from *in vivo* assays were prepared for LC-MS/MS by protein precipitation. Stock solutions of amoxicillin and internal standard moxifloxacin were prepared in methanol at a concentration of 500 μ g/mL. A twelve-point calibration curve was prepared in blank swine serum ranging from 2.5-10000 ng/mL. 100 μ L of each sample was spiked with 200 μ L of 250 ng/mL moxifloxacin in acetonitrile as the internal standard. Samples were centrifuged for 10 minutes at 13,000 rpm. Following centrifugation, 200 μ L of supernatant was pipetted into a 96-well plate containing 200 μ L of water. Analyte concentrations of amoxicillin were analyzed using Ultra-Performance Liquid Chromatography-Tandem Mass Spectrometry (UPLC-MS/MS). Analysis was performed on a Waters ACQUITY UPLC®-I-Class System aligned with a Waters Xevo® TQ-S mass spectrometer (Waters Corporation, Milford MA). Liquid chromatographic separation was performed on either an Acquity UPLC® BEH (50mm $\times$ 2.1mm, 1.7 μ m particle size) column at 50 °C. Sample introduction and ionization were performed by electrospray ionization (ESI) in the positive ionization mode. 10.0 μ L was injected onto the instrument for analysis. For the analysis of amoxicillin, the mobile following mobile phases were used: A (aqueous): 0.1% formic acid, 10mM ammonium formate solution, and B (acetonitrile): 10 mM ammonium formate, 0.1% formic acid solution (95:5 v/v) (Mobile Phase B). The mobile phase had a continuous flow rate of 0.6 mL/min using a time and solvent gradient composition. The initial composition, 100% Mobile Phase

A, was held for 1.00 minutes. Following which, the composition was changed linearly to 50% Mobile Phase A and 50% Mobile Phase B until 1.25 minutes. At 1.50 minutes the composition changed to 20% Mobile Phase A, and at 2.50 minutes the composition was 100% Mobile Phase B. The composition was held constant at 100% Mobile Phase B until 3.00 minutes. At 3.25 minutes the composition returned to 100% Mobile Phase A, where it remained for column equilibration for the duration of the run, ending at 4.00 minutes. Waters MassLynx 4.1 software was used for data acquisition and analysis. The mass to charge transition (m/z) used to quantitate amoxicillin was 366.264>114.112 and 402.21>110.12 for internal standard moxifloxacin.

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INCORPORATION BY REFERENCE

[00230] The present application refers to various issued patent, published patent applications, scientific journal articles, and other publications, all of which are incorporated herein by reference. The details of one or more embodiments of the present disclosure are set forth herein. Other features, objects, and advantages of the present disclosure will be apparent from the Detailed Description, the Figures, the Examples, and the Claims.

EQUIVALENTS AND SCOPE

[00231] In the claims articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[00232] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth in *haec verba* herein. It is also noted that the terms “comprising” and “containing” are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[00233] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims.

Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

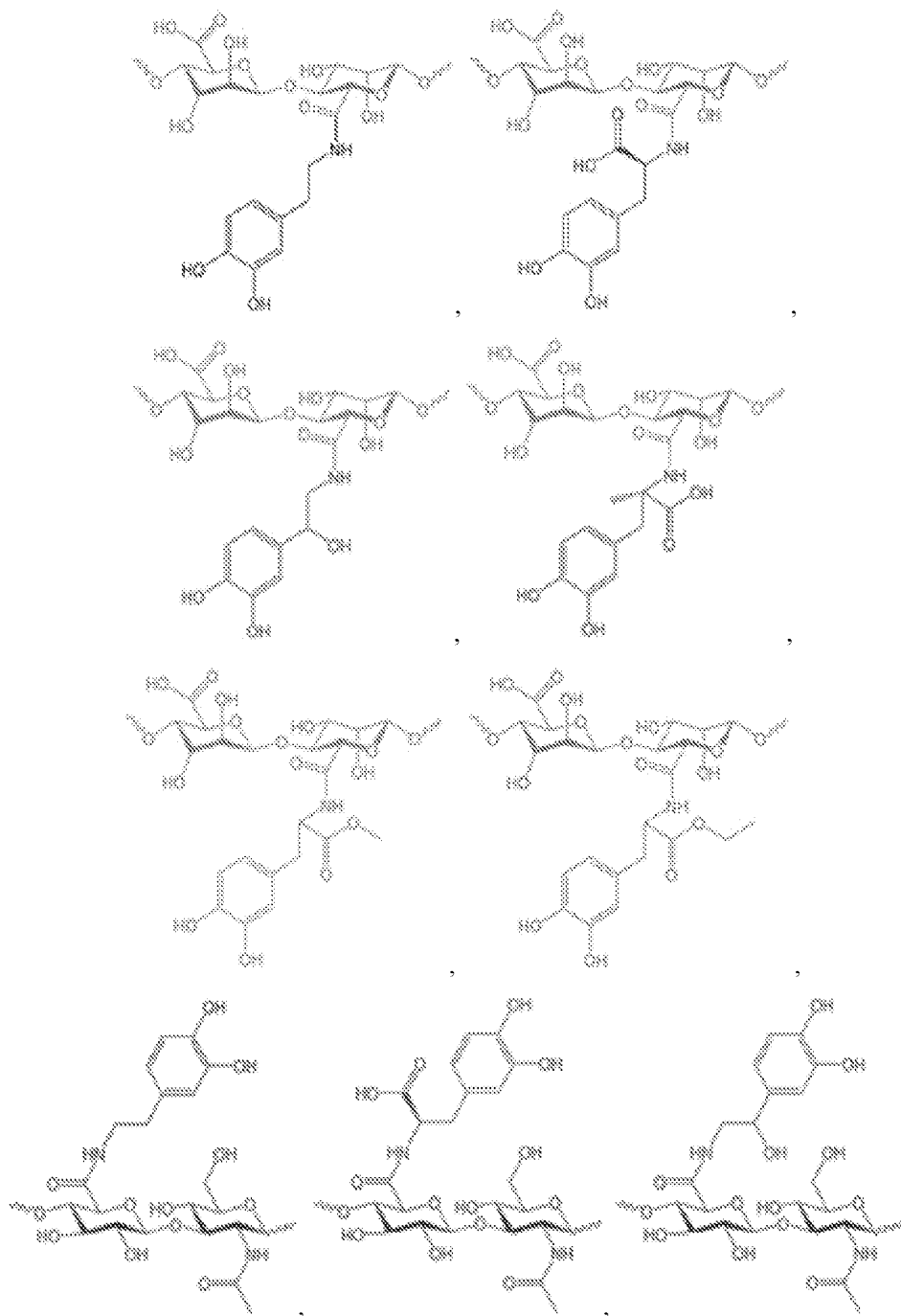
[00234] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

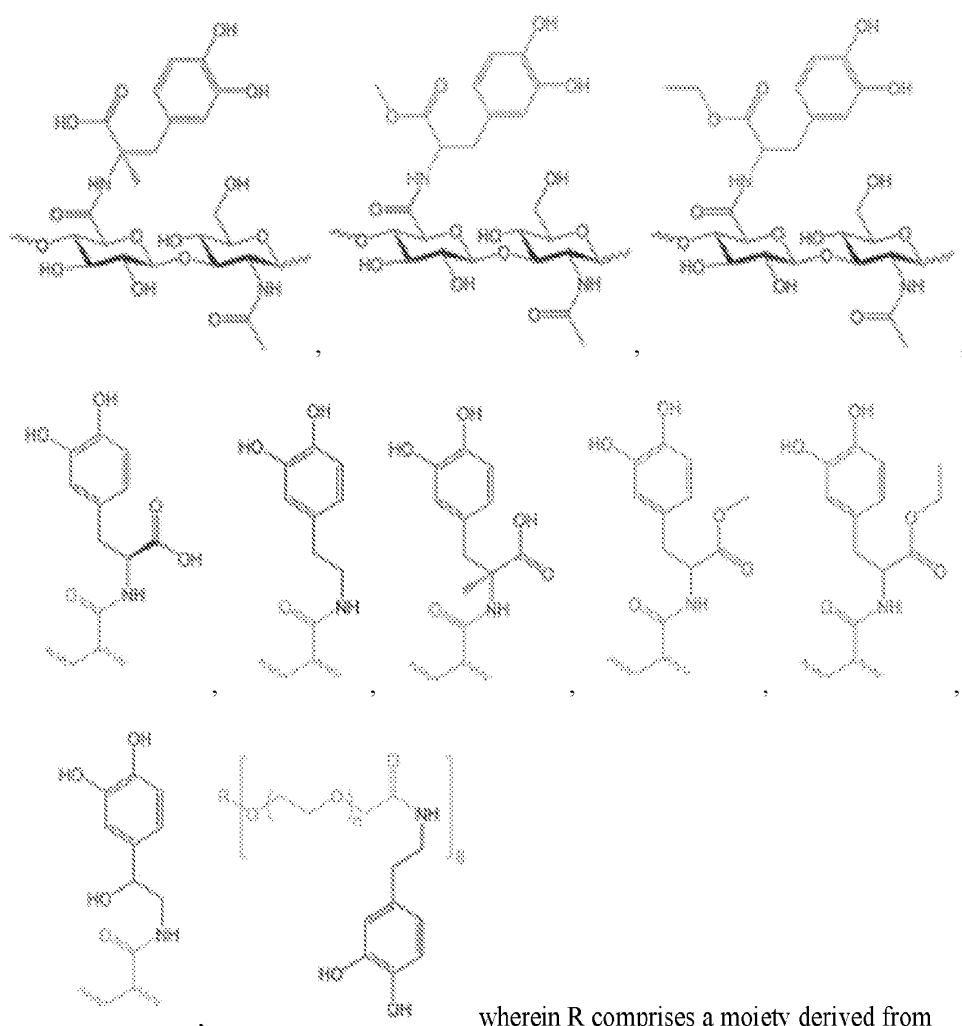
CLAIMS

What is claimed is:

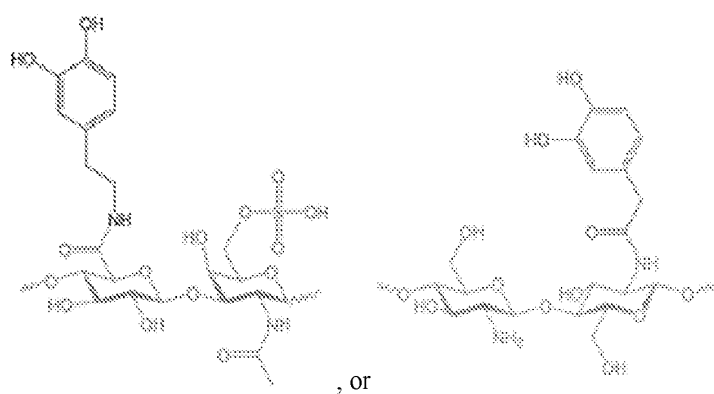
1. A solid oral dosage form comprising a first layer and a second layer wherein:
the first layer comprises a monomer and an oxygen source;
the second layer comprises an active pharmaceutical agent; and
the monomer further comprises a backbone molecule.
2. The solid oral dosage form of claim 1, further comprising a third layer, wherein:
the third layer comprises a monomer and an oxygen source; and
the second layer is disposed between the first and the third layer.
3. The solid oral dosage form of claim 1 or 2, wherein the monomer and the oxygen source of the first layer are the same as the monomer and the oxygen source of the third layer.
4. The solid oral dosage form of any one of claims 1-3, wherein the monomer comprises dopamine, levodopa, norepinephrine, methyl dopa, levodopa methyl ester, levodopa ethyl ester, or a combination thereof.
5. The solid oral dosage form of claim 4, wherein the monomer comprises dopamine.
6. The solid oral dosage form of any one of claims 1-5, wherein the backbone molecule comprises alginate, hyaluronic acid, polyacrylic acid, polyethylene glycol, chondroitin sulfate, chitosan, or a combination thereof.
7. The solid oral dosage form of claim 6, wherein the backbone molecule comprises alginate.
8. The solid oral dosage form of any one of claims 1-7, wherein the monomer is covalently bound to the backbone molecule.

9. The solid oral dosage form of claim 8, wherein the monomer is of the formula:



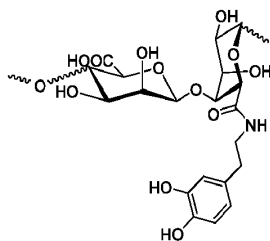


wherein R comprises a moiety derived from tripentaerythritol,



10. The solid oral dosage form of claim 9, wherein the monomer comprises dopamine and the backbone molecule comprises alginate.

11. The solid oral dosage form of claim 10, wherein the monomer is of the formula:



12. The solid oral dosage form of any one of claims 1-11, wherein the monomer consists of a single type of monomer.

13. The solid oral dosage form of any one of claims 1-11, wherein the monomer comprises a combination of monomers.

14. The solid oral dosage form of claim 13, wherein the combination of monomers consists of two or three different monomers.

15. The solid oral dosage form of any one of claims 1-14, wherein the oxygen source is hydrogen peroxide or urea hydrogen peroxide.

16. The solid oral dosage form of claim 15, wherein the oxygen source is hydrogen peroxide.

17. The solid oral dosage form of any one of claims 1-16, wherein the active pharmaceutical agent is a small molecule.

18. The solid oral dosage form of any one of claims 1-16, wherein the active pharmaceutical agent is used to treat an infectious disease, a neurological disease, a pain disorder, a proliferative disease, an autoimmune disease, an inflammatory disease, a metabolic disease, enzymatic deficiency, an immune disorder, or allergies.

19. The solid oral dosage form of claim 18, wherein the infectious disease is a bacterial infection.
20. The solid oral dosage form of claim 18, wherein the infectious disease is a viral infection.
21. The solid oral dosage form of claim 18, wherein the proliferative disease is cancer.
22. The solid oral dosage form of claim 18, wherein the neurological disease is Parkinson's disease.
23. The solid oral dosage form of any one of claims 1-17, wherein the active pharmaceutical is an antibiotic or antiparkinsonism therapeutic.
24. The solid oral dosage form of claim 23, wherein the antibiotic is a penicillin.
25. The solid oral dosage form of claim 23, wherein the antibiotic is amoxicillin.
26. The solid oral dosage form of claim 23, wherein the antiparkinsonism therapeutic comprises levodopa and carbidopa.
27. The solid oral dosage form of any one of claims 1-26, wherein the active pharmaceutical agent has a half-life of less than 24 hours.
28. The solid oral dosage form of any one of claims 1-26, wherein the active pharmaceutical agent has a half-life of less than 12 hours.
29. The solid oral dosage form of any one of claims 1-26, wherein the active pharmaceutical agent has a half-life of less than 6 hours.
30. The solid oral dosage form of any one of claims 1-26, wherein the active pharmaceutical agent is dosed more frequently than once per day.

31. The solid oral dosage form of any one of claims 2-30, wherein the first and third layers further comprise a buffer.
32. The solid oral dosage form of claim 31, wherein the buffer is tris base.
33. The solid oral dosage of any one of claims 1-32, wherein the second layer further comprises a drug release matrix.
34. The solid oral dosage of claim 33, wherein the drug release matrix is hydroxypropyl methyl cellulose (HPMC) matrix.
35. The solid oral dosage of claim 34, wherein the HPMC matrix comprises between about 10 and about 50% HPMC.
36. The solid oral dosage of claim 35, wherein the HPMC matrix comprises about 10% HPMC.
37. The solid oral dosage of claim 35, wherein the HPMC matrix comprises about 20% HPMC.
38. The solid oral dosage of claim 35, wherein the HPMC matrix comprises about 50% HPMC.
39. The solid oral dosage form of any one of claims 2-37, wherein the first and third layers form an exterior portion of the solid oral dosage form.
40. The solid oral dosage form of any one of claims 1-38, further comprising an excipient.
41. The solid oral dosage form of any one of claims 1-39, wherein the solid oral dosage form is in the form of a tablet.
42. The solid oral dosage form of any one of claims 1-40, wherein the second layer is encapsulated by the first layer.

43. The solid oral dosage form of any one of claims 2-40, wherein the second layer is encapsulated by the first and third layers.
44. The solid oral dosage form of any one of claims 1-39, wherein at least a portion of the second layer forms an exterior surface of the solid oral dosage form.
45. The solid oral dosage form of any one of claims 1-43, wherein the tablet is encapsulated by a fourth layer.
46. The solid oral dosage form of claim 44, wherein the fourth layer is an enteric coating.
47. A method of administering an active pharmaceutical ingredient to a subject in need thereof, the method comprising administering to the subject the solid oral dosage form of any one of claims 1-45.
48. A method of reducing the dosing frequency of an active pharmaceutical ingredient in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form of any one of claims 1-45.
49. A method of prolonging gastrointestinal retention of an active pharmaceutical ingredient in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form of any one of claims 1-45.
50. A method of sustaining the release of an active pharmaceutical ingredient in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form of any one of claims 1-45.
51. A method of treating a bacterial infection in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form of any one of claims 1-45.
52. A method of treating infectious disease in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form of any one of claims 1-45.

53. A method of treating a symptom of Parkinson's disease in a subject in need thereof, the method comprising administering to the subject the solid oral dosage form of any one of claims 1-45.
54. A method of increasing the half-life of an active pharmaceutical agent in the subject, the method comprising administering to the subject the solid oral dosage form of any one of claims 1-45.
55. A method of increasing residence time of an active pharmaceutical agent in the subject, the method comprising administering to the subject the solid oral dosage form of any one of claims 1-45.
56. The method of any one of claims 47-54, wherein the solid oral dosage form of any one of claims 1-45 is administered to a subject in need thereof and the oxygen source contacts an endogenous catalyst in a tissue of the subject and release of oxygen from the oxygen source polymerizes the monomer on the tissue.
57. The solid oral dosage form of any one of claims 1-45 or method of any one of claims 46-54, wherein the solid oral dosage forms a polymer *in vivo* in a subject following administration to the subject.
58. The method of claim 55, wherein the polymer forms on the gastrointestinal tract.
59. The method of claim 55, wherein the polymer forms on the small intestine.
60. The method of anyone of any one of claims 55-57, wherein the polymer is in the form of a hydrogel.
61. The method of claim 58, wherein the hydrogel has a concentration of alginate-dopamine (ALG-DA) of about 1-10%.
62. The method of claim 59, wherein the hydrogel has a concentration of ALG-DA of about 4%

63. The method of claim 59, wherein the hydrogel has a concentration of ALG-DA of about 2%

64. A kit comprising:
a solid oral dosage form of any one of claims 1-45, and
instructions for administering the solid oral dosage form to a subject.