GEOMETRIC CONFIGURATIONS FOR GASTRIC RESIDENCE SYSTEMS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of United States Provisional Patent Application No. 62/264,811, filed December 8, 2015. The entire contents of that application are hereby incorporated by reference herein.

FIELD OF THE INVENTION

[0002] The invention relates to systems which remain in the stomach for extended periods for sustained release of pharmaceuticals, and methods of use thereof.

BACKGROUND OF THE INVENTION

[0003] Gastric residence systems are delivery systems for therapeutic agents which remain in the stomach for days to weeks, or even over longer periods, during which time drugs or other agents can elute from the systems for absorption in the gastrointestinal tract. Examples of such systems are described in International Patent Application No. PCT/US2015/035423 (WO 2015/191920); Zhang et al., Nature Materials **14**:1065–1071 (2015); and Bellinger et al., Science Translational Medicine **8**(365): 365ra157 (2016). Gastric residence systems are most conveniently administered to a patient via a capsule in a compacted form. Upon dissolution of the capsule in the stomach, the systems expand to a size which resists passage through the pyloric sphincter over the desired residence period. These characteristics require careful selection of both the materials from which the system is constructed, and the dimensions and arrangement of the system.

[0004] The current invention describes advancements in design and manufacture of gastric residence systems which extend shelf life by, for example, minimizing system stress during storage. The manufacturing methods described herein both lower the cost of manufacture and improve the performance of the systems when administered to a patient.

SUMMARY

[0005] The disclosure provides gastric residence systems, which are administered to the stomach of a patient, for sustained release of a therapeutic agent, and methods of making and using such gastric residence systems.

[0005a] In an aspect of the present disclosure, there is provided a gastric residence system for administration to the stomach of a patient, comprising:

an elastomer component, wherein the elastomer is mono-concave, bi-concave, concavo-convex, or toroidal;

a plurality of at least three carrier polymer-agent components comprising a carrier polymer and a therapeutic agent or a salt thereof,

wherein each of the plurality of carrier polymer-agent components comprises an elongate member comprising a proximal end, a distal end, and an outer surface therebetween;

wherein the proximal end of each elongate member is attached to the elastomer component and projects radially from the elastomer component, each elongate member having its distal end not attached to the elastomer component and located at a larger radial distance from the elastomer component than the proximal end;

wherein the gastric residence system is configured to have a compacted form in a container, suitable for administration orally or through a feeding tube; and an uncompacted form when released from the container in the stomach of the patient;

wherein the gastric residence system is retained in the stomach for a period of at least about 24 hours; and

wherein the system releases a therapeutically effective amount of therapeutic agent over at least a portion of the period in which the system is retained in the stomach.

[0005b] In another aspect of the present disclosure, there is provided a gastric residence system for administration to the stomach of a patient, comprising:

an elastomer component, wherein the elastomer is mono-concave, bi-concave, concavo-convex, or toroidal;

a plurality of at least three carrier polymer-agent components comprising a carrier polymer and a therapeutic agent or a salt thereof,

wherein each of the plurality of carrier polymer-agent components comprises an elongate member comprising a proximal end, a distal end, and an outer surface therebetween;

wherein the proximal end of each elongate member is attached to the elastomer component and projects radially from the elastomer component, each elongate member having its distal end not attached to the elastomer component and located at a larger radial distance from the elastomer component than the proximal end;

wherein the elastomer is attached directly or indirectly to each elongate member by an intercomponent anchor;

wherein the gastric residence system is configured to have a compacted form in a container, suitable for administration orally or through a feeding tube; and an uncompacted form when released from the container in the stomach of the patient;

wherein the gastric residence system is retained in the stomach for a period of at least about 24 hours; and

wherein the system releases a therapeutically effective amount of therapeutic agent over at least a portion of the period in which the system is retained in the stomach.

[0005c] In a further aspect of the present disclosure, there is provided a method of making an elastomer-intercomponent anchor assembly comprising:

overmolding an elastomer component over a first portion of a plurality of at least three intercomponent anchors.

[0005d] In another aspect of the present disclosure, there is provided a method of making an elastomer-intercomponent anchor-interfacing polymer assembly comprising:

overmolding each one of a plurality of interfacing polymer components over a second portion of a corresponding one of the at least three intercomponent anchors of the elastomer-intercomponent anchor assembly disclosed herein.

[0005e] In a further aspect of the present disclosure, there is provided an elastomer-intercomponent anchor assembly comprising:

a plurality of intercomponent anchors comprising a first portion and a second portion; and

an elastomer;

wherein the elastomer covers the first portion of the plurality of intercomponent anchors.

[0005f] In another aspect of the present disclosure, there is provided an elastomer-intercomponent anchor-interfacing polymer assembly comprising:

a plurality of interfacing polymer components covering the second portion of a corresponding one of the at least three intercomponent anchors of the elastomer-intercomponent anchor assembly disclosed herein.

[0005g] In a further aspect of the present disclosure, there is provided a method of making a gastric residence system assembly comprising:

a) overmolding an elastomer component over a first portion of a plurality of at least three intercomponent anchors; and

b) overmolding a plurality of interfacing polymer components over a second portion of each intercomponent anchor, wherein each interfacing polymer component is overmolded over a corresponding one of the at least three intercomponent anchors.

[0005h] In another aspect of the present disclosure, there is provided a gastric residence system for administration to the stomach of a patient, comprising: an elastomer component, wherein the elastomer is bi-concave or concavo-convex; a plurality of at least three carrier polymer-agent components comprising a carrier polymer and a therapeutic agent or a salt thereof, wherein each of the plurality of carrier polymer-agent components is an elongate member comprising a proximal end, a distal end, and an outer surface therebetween; wherein the proximal end of each elongate member is attached to the elastomer component and projects radially from the elastomer component, each elongate member having its distal end not attached to the elastomer component and located at a larger radial distance from the elastomer component than the proximal end; wherein the gastric residence system is configured to have a compacted form in a container, suitable for administration orally or through a feeding tube; and an uncompacted form when released from the container in the stomach of the patient; wherein the gastric residence system is retained in the stomach for a period of at least about 24 hours; and wherein the system releases a therapeutically effective amount of therapeutic agent over at least a portion of the period in which the system is retained in the stomach.

[0006] In one example, the disclosure provides gastric residence systems for administration to the stomach of a patient, comprising an elastomer component, wherein the elastomer can be mono-concave, bi-concave, concavo-convex, or toroidal; a plurality of at least three carrier polymer-agent components comprising a carrier polymer and a therapeutic agent or a salt thereof, wherein each of the plurality of carrier polymer-agent components comprises an elongate member comprising a proximal end, a distal end, and an outer surface therebetween; wherein the proximal end of each elongate member can be attached to the elastomer component and projects radially from the elastomer component, each elongate member having its distal end not attached to the elastomer component and located at a larger radial distance from the elastomer component than the proximal end; wherein the elastomer can be attached directly or indirectly to each elongate member by an intercomponent anchor; wherein the gastric residence system can be configured to have a compacted form in a container, suitable for administration orally or through a feeding tube; and an uncompacted form when released from the container in the stomach of the patient; wherein the gastric residence system is retained in the stomach for a

period of at least about 24 hours; and wherein the system releases a therapeutically effective amount of therapeutic agent over at least a portion of the period in which the system is retained in the stomach.

[0007] In some examples, the gastric residence systems have a first portion of each intercomponent anchor located within the elastomer, and a second portion of each intercomponent anchor located within either a) a corresponding first segment of interfacing polymer, wherein each corresponding first segment of interfacing polymer is also attached directly or indirectly to a corresponding one of the elongate members; or b) a corresponding segment of linker, wherein each corresponding segment of linker is also attached directly or indirectly to a corresponding one of the elongate members; or c) a corresponding one of the elongate members. In some examples, the gastric residence systems can have a first portion of each intercomponent anchor located within the elastomer, and a second portion of each intercomponent anchor is located within a corresponding first segment of interfacing polymer, wherein each corresponding first segment of interfacing polymer is also attached to a corresponding linker, such as an enteric linker or time-dependent linker, and each corresponding linker (such as an enteric linker or time-dependent linker) is attached to a corresponding one of the elongate members.

[0008] In some examples of the gastric residence systems, a first portion of each intercomponent anchor is located within the elastomer, and a second portion of each intercomponent anchor is located within a corresponding first segment of interfacing polymer, wherein each corresponding first segment of interfacing polymer is also attached to a corresponding linker, such as an enteric linker or time-dependent linker, wherein each corresponding linker (such as an enteric linker or time-dependent linker) is attached to a corresponding second segment of interfacing polymer; and each corresponding second segment of interfacing polymer is attached to a corresponding one of the elongate members.

[0009] In any of the examples of the gastric residence systems described herein, the linkers can comprise hydroxypropyl methyl cellulose acetate succinate (HPMCAS) and polycaprolactone (PCL); that is, the linkers can be enteric linkers. The ratio of HPMCAS to polycaprolactone can be between about 80% HPMCAS:20% PCL to about 20% HPMCAS:80% PCL. The linker can further comprise a plasticizer selected from the group consisting of triacetin, triethyl citrate, tributyl citrate, poloxamers, polyethylene glycol, polypropylene glycol, diethyl phthalate, dibutyl sebacate, glycerin, castor oil, acetyl triethyl citrate, acetyl tributyl citrate, polyethylene glycol monomethyl ether, sorbitol, sorbitan, a sorbitol-sorbitan mixture, and diacetylated monoglycerides.

[0010] In any of the examples of the gastric residence systems described herein which use intercomponent anchors, the elastomer can be overmolded over the first portions of the intercomponent anchors. In any of the examples of the gastric residence systems described herein which use intercomponent anchors, the first segment of each interfacing polymer, linker, or elongate member can be overmolded over the corresponding second portion of the intercomponent anchors.

[0011] In any of the examples of the gastric residence systems described herein, the elastomer can comprise a material selected from the group comprising silicone rubber, a polysiloxane, polydimethylsiloxane, silicone rubber mixed with silica, a polysiloxane mixed with silica, and polydimethylsiloxane mixed with silica. The elastomer can comprise silicone rubber. The elastomer can comprise a polysiloxane. The elastomer can comprise polydimethylsiloxane. The elastomer can comprise silicone rubber mixed with silica. The elastomer can comprise a polysiloxane mixed with silica. The elastomer can comprise polydimethylsiloxane mixed with silica.

[0012] In any of the examples of the gastric residence systems described herein which use intercomponent anchors, the intercomponent anchors can comprise a material selected from the group consisting of polycarbonate, polyphenylsulfone, a polyphenylene ether-polystyrene blend, polyphenylene ether, polystyrene, and polyether ether ketone.

[0013] In any of the examples of the gastric residence systems described herein, the elastomer can be mono-concave, bi-concave, concavo-convex, or toroidal. The elastomer can be mono-concave. The elastomer can be bi-concave. The elastomer can be concavo-convex. The elastomer can be toroidal. In any of the examples of the gastric residence systems described herein, the elastomer can be bi-concave or concavo-convex. The elastomer can be bi-concave. The elastomer can be concavo-convex.

[0014] In any of the examples of the gastric residence systems described herein, the elastomer can be asterisk-shaped. The center of the asterisk comprises the mono-concave, bi-concave, or concavo-convex portion of the corresponding mono-concave, bi-concave, or concavo-convex elastomer.

[0015] In any of the examples of the gastric residence systems described herein, the elastomer can comprise a material which has a compression set of less than about 15%. In any of the examples of the gastric residence systems described herein, the elastomer can comprise a material which has a tear strength greater than about 20 kN/m. In any of the examples of the gastric residence systems described herein, the elastomer can comprise a material which has a compression set of less than about 15% and a tear strength greater than about 20 kN/m.

[0016] In any of the examples of the gastric residence systems described herein, the gastric residence system can have a folding force of at least about 0.2 newtons. In any of the examples of the gastric residence systems described herein, the gastric residence system can have a folding force of at least about 0.2 newtons when the elongate members are at an angle between about 0 degrees and about 70 degrees from the fully unfolded plane of the system. In any of the examples of the gastric residence systems described herein, the maximum folding force of the gastric residence system can occur when the elongate members are at an angle between about 0 degrees and about 70 degrees from the fully unfolded plane of the system.

[0017] In any of the examples of the gastric residence systems described herein, the gastric residence system has an x-y bending force of at least about 0.2 newtons. In any of the examples of the gastric residence systems described herein, the gastric residence system has

an x-y bending force of at least about 0.2 newtons when the arms are bent more than about 5 degrees from the position occupied when not subjected to an x-y bending force. In any of the examples of the gastric residence systems described herein, the gastric residence system has an x-y bending force of at least about 0.2 newtons when the arms are bent more than about 10 degrees from the position occupied when not subjected to an x-y bending force.

[0018] In any of the examples of the gastric residence systems described herein, the elastomer can be formed by injection molding.

[0019] In any of the examples of the gastric residence systems described herein, the plurality of carrier polymer-agent components can have a triangular cross-section. Triangular cross-sections include triangular cross-sections with rounded or filleted edges and corners.

[0020] In any of the examples of the gastric residence systems described herein, the elastomer can be asterisk-shaped and the branches of the asterisk can have a triangular cross-section. Triangular cross-sections include triangular cross-sections with rounded or filleted edges and corners.

[0021] In any of the examples of the gastric residence systems described herein, the plurality of carrier polymer-agent components can comprise between four and eight carrier polymer-agent components inclusive, between five and seven carrier polymer-agent components inclusive, or six carrier polymer-agent components.

[0022] In some examples, the disclosure provides gastric residence systems for administration to the stomach of a patient, comprising an elastomer component, wherein the elastomer is mono-concave, bi-concave, concavo-convex, or toroidal; a plurality of at least three carrier polymer-agent components comprising a carrier polymer and a therapeutic agent or a salt thereof, wherein each of the plurality of carrier polymer-agent components can comprise an elongate member comprising a proximal end, a distal end, and an outer surface therebetween; wherein the proximal end of each elongate member is attached to the elastomer component and projects radially from the elastomer component, each elongate member having its distal end not attached to the elastomer component and located at a larger radial distance from the elastomer component than the proximal end; wherein the gastric residence system is configured to have a compacted form in a container, suitable for administration orally or through a feeding tube; and an uncompacted form when released from the container in the stomach of the patient; wherein the gastric residence system is retained in the stomach for a period of at least about 24 hours; and wherein the system releases a therapeutically effective amount of therapeutic agent over at

least a portion of the period in which the system is retained in the stomach. In some examples, the proximal end of each elongate member can be directly attached to the elastomer component. In some examples, the proximal end of each elongate member can be indirectly attached to the elastomer component. In some examples, the elastomer can be bi-concave. In some examples, the elastomer can be mono-concave. In some examples, the elastomer can be concavo-convex. In some examples, the elastomer can be toroidal.

[0023] In any of the examples of the gastric residence systems described herein, the elastomer can comprise a material which has a compression set of less than about 15%. In any of the examples of the gastric residence systems described herein, the elastomer can comprise a material which has a tear strength greater than about 20 kN/m. In any of the examples of the gastric residence systems described herein, the elastomer can comprise a material which has a compression set of less than about 15% and a tear strength greater than about 20 kN/m.

[0024] In some examples, the gastric residence system can have a folding force of at least about 0.2 newtons when the elongate members are at an angle between about 0 degrees and about 70 degrees from the fully unfolded plane of the system. In some examples, wherein the maximum folding force of the gastric residence system occurs when the elongate members are at an angle between about 0 degrees and about 70 degrees from the fully unfolded plane of the system.

[0025] In any of the examples of the gastric residence systems described herein, the gastric residence system has an x-y bending force of at least about 0.2 newtons. In any of the examples of the gastric residence systems described herein, the gastric residence system has an x-y bending force of at least about 0.2 newtons when the arms are bent more than about 5 degrees from the position occupied when not subjected to an x-y bending force. In any of the examples of the gastric residence systems described herein, the gastric residence system has an x-y bending force of at least about 0.2 newtons when the arms are bent more than about 10 degrees from the position occupied when not subjected to an x-y bending force.

[0026] In any of the examples of the gastric residence systems described herein, the gastric residence system has a folding force of at least about 0.2 newtons, and an x-y bending force of at least about 0.2 newtons. In any of the examples of the gastric residence systems, the x-y bending force required to bend the structure is at least about 0.2 Newtons (N), at least about 0.3 N, at least about 0.4 N, at least about 0.5 N, at least about 0.75 N, at least about 1 N, at

least about 1.5 N, at least about 2 N, at least about 2.5 N, at least about 3 N, at least about 4 N, or at least about 5 N; and the folding force required to fold the structure is at least about 0.2 Newtons (N), at least about 0.3 N, at least about 0.4 N, at least about 0.5 N, at least about 0.75 N, at least about 1 N, at least about 1.5 N, at least about 2 N, at least about 2.5 N, at least about 3 N, at least about 4 N, or at least about 5 N. In any of the examples of the gastric residence systems, the x-y bending force required to bend the structure is at least about 0.2 N; and the folding force required to fold the structure is at least about 0.2 N. In any of the examples of the gastric residence systems, the x-y bending force required to bend the structure is at least about 0.2 N; and the folding force required to fold the structure is at least about 0.3 N. In any of the examples of the gastric residence systems, the x-y bending force required to bend the structure is at least about 0.3 N; and the folding force required to fold the structure is at least about 0.2 N. In any of the examples of the gastric residence systems, the x-y bending force required to bend the structure is at least about 0.2 N; and the folding force required to fold the structure is at least about 0.4 N. In any of the examples of the gastric residence systems, the x-y bending force required to bend the structure is at least about 0.4 N; and the folding force required to fold the structure is at least about 0.2 N. In any of the examples of the gastric residence systems, the x-y bending force required to bend the structure is at least about 0.4 N; and the folding force required to fold the structure is at least about 0.4 N. In any of the examples, the x-y bending force required to bend the structure is between about 0.2 N to about 5 N, between about 0.3 N to about 5 N, between about 0.4 N to about 5 N, between about 0.5 N to about 5 N, between about 0.75 N to about 5 N, between about 1 N to about 5 N, between about 1.5 N to about 5 N, between about 2 N to about 5 N, between about 2.5 N to about 5 N, between about 3 N to about 5 N, or between about 4 N to about 5 N; and the folding force required to fold the structure is between about 0.2 N to about 5 N, between about 0.3 N to about 5 N, between about 0.4 N to about 5 N, between about 0.5 N to about 5 N, between about 0.75 N to about 5 N, between about 1 N to about 5 N, between about 1.5 N to about 5 N, between about 2 N to about 5 N, between about 2.5 N to about 5 N, between about 3 N to about 5 N, or between about 4 N to about 5 N. In any of the examples, the x-y bending force required to bend the structure is between about 0.2 N to about 4 N, between about 0.3 N to about 4 N, between about 0.4 N to about 4 N, between about 0.5 N to about 4 N, between about 0.75 N to about 4 N, between about 1 N to about 4 N, between about 1.5 N to about 4 N, between about 2 N to about 4 N, between about 2.5 N to about 4 N, between about 3 N to about 4 N, or between

about 3.5 N to about 4 N; and the folding force required to fold the structure is between about 0.2 N to about 4 N, between about 0.3 N to about 4 N, between about 0.4 N to about 4 N, between about 0.5 N to about 4 N, between about 0.75 N to about 4 N, between about 1 N to about 4 N, between about 1.5 N to about 4 N, between about 2 N to about 4 N, between about 2.5 N to about 4 N, between about 3 N to about 4 N, or between about 3.5 N to about 4 N. In any of the examples, the x-y bending force required to bend the structure is between about 0.2 N to about 4 N, between about 0.2 N to about 3.5 N, between about 0.2 N to about 3 N, between about 0.2 N to about 2.5 N, between about 0.2 N to about 2 N, between about 0.2 N to about 1.5 N, between about 0.2 N to about 1 N, between about 0.2 N to about 0.75 N, between about 0.2 N to about 0.5 N, between about 0.2 N to about 0.4 N, or between about 0.2 N to about 0.3 N; and the folding force required to fold the structure is between about 0.2 N to about 4 N, between about 0.2 N to about 3.5 N, between about 0.2 N to about 3 N, between about 0.2 N to about 2.5 N, between about 0.2 N to about 2 N, between about 0.2 N to about 1.5 N, between about 0.2 N to about 1 N, between about 0.2 N to about 0.75 N, between about 0.2 N to about 0.5 N, between about 0.2 N to about 0.4 N, or between about 0.2 N to about 0.3 N.

[0027] In any of the examples of the gastric residence systems described herein, the elastomer can comprise a material selected from the group comprising silicone rubber, a polysiloxane, polydimethylsiloxane, silicone rubber mixed with silica, a polysiloxane mixed with silica, and polydimethylsiloxane mixed with silica. The elastomer can be formed by injection molding.

[0028] In any of the examples of the gastric residence systems described herein, the plurality of carrier polymer-agent components can have a triangular cross-section. Triangular cross-sections include triangular cross-sections with rounded or filleted edges and corners.

[0029] In any of the examples of the gastric residence systems described herein, the elastomer can be asterisk-shaped and the branches of the asterisk can have a triangular cross-section. Triangular cross-sections include triangular cross-sections with rounded or filleted edges and corners.

[0030] In any of the examples of the gastric residence systems described herein, the plurality of carrier polymer-agent components can comprise between four and eight carrier polymer-agent components inclusive, between five and seven carrier polymer-agent components inclusive, or six carrier polymer-agent components.

[0031] In some examples, the disclosure provides a method of making an elastomer-intercomponent anchor assembly, comprising overmolding an elastomer component over a first portion of a plurality of at least three intercomponent anchors. In some examples, the method further comprises overmolding each one of a plurality of interfacing polymer components over a second portion of a corresponding one of the at least three intercomponent anchors of the elastomer-intercomponent anchor assembly. That is, each second portion of each intercomponent anchor is overmolded with a separate interfacing polymer component, such that the number of interfacing polymer components is equal to the number of intercomponent anchors.

[0032] In some examples, the disclosure provides an elastomer-intercomponent anchor assembly, comprising a plurality of intercomponent anchors comprising a first portion and a second portion; and an elastomer, wherein the elastomer covers the first portion of the plurality of intercomponent anchors. In some examples, the disclosure provides an elastomer-intercomponent anchor-interfacing polymer assembly comprising a plurality of interfacing polymer components covering the second portion of a corresponding one of the at least three intercomponent anchors of the elastomer-intercomponent anchor assembly. That is, each second portion of each intercomponent anchor is covered by a separate interfacing polymer component, such that the number of interfacing polymer components is equal to the number of intercomponent anchors.

[0033] In some examples, the disclosure provides a method of making a gastric residence system assembly, comprising overmolding an elastomer component over a first portion of a plurality of at least three intercomponent anchors; and overmolding a plurality of interfacing polymer components over a second portion of each intercomponent anchor, wherein each interfacing polymer component is overmolded over a corresponding one of the at least three intercomponent anchors. That is, each second portion of each intercomponent anchor is overmolded with a separate interfacing polymer component, such that the number of interfacing polymer components is equal to the number of intercomponent anchors.

[0034] In any of the examples described herein, the overmolding of the elastomer component and the overmolding of the interfacing polymer components can be performed by injection molding. In any of the examples described herein, the intercomponent anchors can comprise a material selected from the group consisting of polycarbonate, polyphenylsulfone, a polyphenylene ether-polystyrene blend, polyphenylene ether, polystyrene, and polyether ether

ketone. In any of the examples described herein, the elastomer component can comprise a material selected from the group comprising silicone rubber, a polysiloxane, polydimethylsiloxane, silicone rubber mixed with silica, a polysiloxane mixed with silica, and polydimethylsiloxane mixed with silica.

[0035] In some examples of the method, the plurality of intercomponent anchors can be connected by a first scaffold, where the first scaffold maintains the anchors in a desired position prior to overmolding the elastomer component. In some examples of the method, the method further comprises removing the first scaffold after overmolding the elastomer component.

[0036] In some examples of the method, the overmolded plurality of interfacing polymer components can be connected by a second scaffold formed during the overmolding of the interfacing polymer components, where the second scaffold maintains the interfacing polymer components in a desired position. In some examples of the method, the method further comprises removing the second scaffold after overmolding the interfacing polymer components.

[0037] In some examples of the method, the method further comprises trimming the interfacing polymer components to a radial length of about 1 mm to 5 mm. That is, the length of the interfacing polymer components, when measured from the point most proximal to the elastomer to the point most distal from the elastomer, can be trimmed to about 1 mm to about 5 mm.

[0038] In some examples of the method, the method further comprises attaching a plurality of linkers to the plurality of interfacing polymer components, wherein each one of the linkers can be attached to a corresponding one of the interfacing polymer components. In any of the examples described herein, the linkers can be enteric linkers or time-dependent linkers.

[0039] In some examples of the method, the method further comprises attaching a plurality of carrier polymer-agent components to the plurality of linkers, wherein each one of the carrier polymer-agent components can be attached to a corresponding one of the linkers, to form the gastric residence system.

[0040] In some examples, the disclosure provides a method of forming a gastric residence system, comprising comprising attaching a plurality of interfacing polymer-(carrier polymer-agent) components to the plurality of linkers, wherein each one of the interfacing polymer-(carrier polymer-agent) components can be attached to a corresponding one of the linkers, to form the gastric residence system.

[0041] In any example of the method described herein, the attaching of a first component to a second component can be performed by heat welding. The heat welding can be performed by contacting a first component with a heated object (such as a heated platen) at a first temperature to form a heated surface on the first component, contacting a second component with a heated object (such as a heated platen) at a second temperature to form a heated surface on the second component, and contacting the heated surface of the first component with the heated surface of the second component to form a heat weld between the first component and the second component. The method can further comprise applying pressure during the contacting step.

[0042] In some examples of the method described herein, the attaching of a linker to a carrier polymer-agent component (or to an interfacing polymer-(carrier polymer-agent) component) can be performed by heat welding. The heat welding can be performed by contacting each linker with a heated object (such as a heated platen) at a first temperature to form a heated surface on the linker, contacting each carrier polymer-agent component (or each interfacing polymer-(carrier polymer-agent) component) with a heated object (such as a heated platen) at a second temperature to form a heated surface on the carrier polymer-agent component, and contacting the heated surface of the linker with the heated surface of the carrier polymer-agent component (or the heated surface of the interfacing polymer-(carrier polymer-agent) component) to form a heat weld between each linker and each corresponding carrier polymer-agent component (or each interfacing polymer-(carrier polymer-agent) component).

[0043] In any example of the method where a first component is attached to a second component by heat welding, the method can further comprise annealing the heat weld. The annealing can be performed by heating the gastric residence system in an oven at a third temperature. The annealing can be performed by irradiating the heat weld with infrared radiation.

[0044] In any example of the method described herein, the attaching of a first component to a second component can be performed by infrared welding. In any example of the method where a first component is attached to a second component by infrared welding, the method can further comprise annealing the infrared weld. The annealing can be performed by heating the gastric residence system in an oven. The annealing can be performed by irradiating the infrared weld with infrared radiation.

[0045] In any of the examples of the gastric residence systems described herein, the elastomer component can comprise a plurality of branches equal in number to the plurality of at least three carrier polymer-agent components attached to the elastomer, and the elastomer further can comprise webbing between the plurality of branches.

[0046] In any of the examples of the elastomer-intercomponent anchor assembly or the elastomer-intercomponent anchor-interfacing polymer assembly, the elastomer component can comprise a plurality of branches (where the plurality of branches is equal in number to the plurality of at least three carrier polymer-agent components to be attached directly or indirectly to the elastomer), and the elastomer further can comprise webbing between the plurality of branches.

[0047] In one example, the disclosure provides a gastric residence system for administration to the stomach of a patient, said gastric residence system comprising an elastomer component, a plurality of at least three carrier polymer-agent components comprising a carrier polymer and a therapeutic agent or a salt thereof, wherein each of the plurality of carrier polymer-agent components is an elongate member comprising a proximal end, a distal end, and a curved outer surface therebetween; wherein the proximal end of each elongate member is attached to the elastomer and projects radially from the elastomer, each elongate member having its distal end not attached to the elastomer and located at a larger radial distance from the elastomer than the proximal end; wherein the gastric residence system is configured to have a compacted form in a container, suitable for administration orally or through a feeding tube; and an uncompacted form when released from the container in the stomach of the patient; wherein the gastric residence system is retained in the stomach for a period of at least about 24 hours; and wherein the system releases a therapeutically effective amount of therapeutic agent over at least a portion of the period in which the system is retained in the stomach.

[0048] In some examples, a separation angle between one elongate member of the plurality of at least three carrier polymer-agent components to a nearest adjacent other elongate member is approximately equal for each elongate member.

[0049] In some examples, each elongate member is comprised of at least two segments, each segment comprising a proximal end, a distal end, and a curved outer surface therebetween, where the segments are linked together by an enteric polymer, and the enteric polymer is

adherent to a distal end of a first segment and an adjacent proximal end of a second segment, thereby joining the first and second segments.

[0050] In some examples, each elongate member is comprised of at least two segments, each segment comprising a proximal end, a distal end, and a curved outer surface therebetween, where the segments are linked together by an enteric polymer, and the enteric polymer is a film wrapped around a distal portion of the curved outer surface of a first segment and an adjacent proximal portion of the curved outer surface of a second segment, thereby forming a collar joint between the first and second segments.

[0051] In some examples wherein each elongate member is comprised of at least two segments, the distal end of the first segment is concave and the adjacent proximal end of the second segment is convex, or the distal end of the first segment is convex and the adjacent proximal end of the second segment is concave.

[0052] In some examples where the enteric polymer is adherent to a distal end of a first segment and an adjacent proximal end of a second segment, the enteric polymer adherent to the ends of the segments extends beyond the area between the ends of the segments.

[0053] In some examples, the enteric polymer is selected from the group consisting of poly(methacrylic acid-co-ethyl acrylate), cellulose acetate phthalate, cellulose acetate succinate, and hydroxypropyl methylcellulose phthalate.

[0054] In any of the examples of the gastric residence system, the carrier polymer can comprise polycaprolactone.

[0055] In any of the examples of the gastric residence system, the elastomer can comprise cross-linked polycaprolactone.

[0056] In any of the examples of the gastric residence system, the gastric residence system can measure at least about 2 cm in length over at least two perpendicular directions.

[0057] In any of the examples of the gastric residence system, the carrier polymer-agent components can be produced by hot melt extrusion.

[0058] In any of the examples of the gastric residence system, the therapeutic agent or a salt thereof can comprise particles, wherein at least about 80% of the mass of particles have sizes between about 2 microns and about 50 microns in diameter. The particles can be crystalline or amorphous.

[0059] In any of the examples of the gastric residence system, the elastomer component can have the approximate shape of an oblate ellipsoid, that is, a disk.

[0060] In any of the examples of the gastric residence system, the elastomer component can have an approximately asterisk shape, wherein the asterisk shape has at least three branches, and the proximal end of each elongate member is attached to a different branch of the elastomer.

[0061] In further examples, the disclosure provides a gastric residence system according to any example described herein, wherein the gastric residence system is in its compacted form in a container or capsule.

[0062] In further examples, the disclosure provides a method of making a gastric residence system, comprising forming an elastomer component; forming a plurality of at least three carrier polymer-agent components, which are elongate members comprising a proximal end and a distal end; and attaching the elongate members to the elastomer component. The method can further comprise compacting the gastric residence system and inserting the system into a container suitable for oral administration or administration through a gastric tube or feeding tube.

[0063] In the method of making the systems, forming a plurality of at least three carrier polymer-agent components which are elongate members can comprise forming the elongate members from at least two segments. Forming the elongate members from at least two segments can comprise forming a collar joint between the segments.

[0064] In the method of making the systems, the elastomer component can be asterisk-shaped with a plurality of at least three branches.

[0065] In the method of making the systems, attaching the elongate members to the elastomer component can comprise adhering the elongate members to the elastomer component.

[0066] In the method of making the systems, attaching the elongate members to the elastomer component can comprise forming a collar joint between the elongate members and the branches of the asterisk-shaped elastomer component.

[0067] In further examples, the disclosure provides methods of administering a therapeutic agent to a patient, comprising administering a gastric residence system according to any of the examples disclosed herein. In some examples, the gastric residence system has a gastric retention period of about D days, and a new gastric residence system is administered to the patient every D days over a total desired treatment period. The gastric retention period can be about three days, about five days, about seven days, about fourteen days, or about thirty days.

[0068] This disclosure provides several embodiments and examples. It is contemplated that any features from any embodiment and/or examples can be combined with any features from any other embodiment and/or example where

possible. In this fashion, hybrid configurations of the disclosed features are within the scope of the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0069] FIG. 1 shows one embodiment of a gastric residence system of the invention.

[0070] FIG. 2 shows another embodiment of a gastric residence system of the invention.

[0071] FIG. 2A shows another embodiment of a gastric residence system of the invention.

[0072] FIG. 2B shows certain dimensions of the gastric residence system of FIG. 2B.

[0073] FIG. 2C shows the embodiment of a gastric residence system of FIG.2 in a folded configuration. The capsule holding the system in the folded configuration is not shown.

[0074] FIG. 3, panels 3A, 3B, 3C, and 3D show additional embodiments of gastric residence systems of the invention, with varying radial dimensions.

[0075] FIG. 4A shows one embodiment of the system using a bi-concave disk for the central elastomer.

[0076] FIG. 4B is a solid depiction of the two-dimensional depiction of FIG. 4A.

[0077] FIG. 4C is a further solid depiction of the two-dimensional depiction of FIG. 4A.

[0078] FIG. 4D is a side view of the depiction of FIG. 4C.

[0079] FIG. 5A shows another embodiment of the system using a concavo-convex disk for the central elastomer.

[0080] FIG. 5B is a solid depiction of the two-dimensional depiction of FIG. 5A.

[0081] FIG. 5C is a further solid depiction of the two-dimensional depiction of FIG. 5A.

[0082] FIG. 5D is a side view of the depiction of FIG. 5C.

[0083] FIG. 6, with views 6A, 6B, 6B1, 6C, and 6D, shows different embodiments for coupling of segments of carrier polymer-agent component in the arms of the system.

[0084] FIGS. 7A and 7B show enteric linker adhesion as a function of solvent used to wet the enteric linker for adhesion to polymer sheets.

[0085] FIGS. 8A, 8B and 8C show different shapes for the carrier polymer-agent component arms of some embodiments of the system.

[0086] FIG. 9, panels A, B, and C, shows four-point bending flexural tests for single layer and collar Plastoid B and Triacetin enteric linkers. Panel A shows the flexural test arrangement for

CLAIMS

What is claimed is:

1. A gastric residence system for administration to the stomach of a patient, comprising:

an elastomer component, wherein the elastomer is mono-concave, bi-concave, concavo-convex, or toroidal;

a plurality of at least three carrier polymer-agent components comprising a carrier polymer and a therapeutic agent or a salt thereof,

wherein each of the plurality of carrier polymer-agent components comprises an elongate member comprising a proximal end, a distal end, and an outer surface therebetween;

wherein the proximal end of each elongate member is attached to the elastomer component and projects radially from the elastomer component, each elongate member having its distal end not attached to the elastomer component and located at a larger radial distance from the elastomer component than the proximal end;

wherein the gastric residence system is configured to have a compacted form in a container, suitable for administration orally or through a feeding tube; and an uncompacted form when released from the container in the stomach of the patient;

wherein the gastric residence system is retained in the stomach for a period of at least about 24 hours; and

wherein the system releases a therapeutically effective amount of therapeutic agent over at least a portion of the period in which the system is retained in the stomach.

2. The gastric residence system of claim 1, wherein the elastomer component comprises a material which has a compression set of less than about 15%.

3. The gastric residence system of claim 1 or 2, wherein the elastomer component comprises a material which has a tear strength greater than about 20 kN/m.

4. The gastric residence system of any one of claims 1-3, wherein the gastric residence system has a folding force of at least about 0.2 newtons when the elongate members are at an angle between about 0 degrees and about 70 degrees from the fully unfolded plane of the system.

5. The gastric residence system of any one of claims 1-4, wherein the maximum folding force of the gastric residence system occurs when the elongate members are at an angle between about 0 degrees and about 70 degrees from the fully unfolded plane of the system.

6. The gastric residence system of any one of claims 1-5, wherein the gastric residence system has an x-y bending force of at least about 0.2 newtons.

7. The gastric residence system of any one of claims 1-6, wherein the elastomer component comprises a material selected from the group comprising silicone rubber, a polysiloxane, polydimethylsiloxane, silicone rubber mixed with silica, a polysiloxane mixed with silica, and polydimethylsiloxane mixed with silica.

8. The gastric residence system of any one of claims 1-7, wherein the elastomer component is formed by injection molding.

9. The gastric residence system of any one of claims 1-8, wherein the plurality of carrier polymer-agent components have a triangular cross-section.

10. The gastric residence system of any one of claims 1-9, wherein the plurality of carrier polymer-agent components comprises between four and eight carrier polymer-agent components.

11. The gastric residence system of any one of claims 1-10, wherein the elastomer component comprises a plurality of branches equal in number to the plurality of at least three carrier polymer-agent components, and the elastomer component further comprises webbing between the plurality of branches.

12. The gastric residence system of any one of claims 1-11, wherein the therapeutic agent is selected from the group consisting of risperidone, aripiprazole, rosuvastatin, meloxicam, escitalopram, citalopram, clopidogrel, prednisone, buprenorphine, naloxone, montelukast, memantine, digoxin, tamsulosin, ezetimibe, colchicine, loratadine, cetirizine, loperamide,

omeprazole, entecavir, doxycycline, ciprofloxacin, azithromycin, levothyroxine, methadone, varenicline, contraceptives, olanzapine, donezepil, and ivermectin.

13. A gastric residence system for administration to the stomach of a patient, comprising:

an elastomer component, wherein the elastomer is mono-concave, bi-concave, concavo-convex, or toroidal;

a plurality of at least three carrier polymer-agent components comprising a carrier polymer and a therapeutic agent or a salt thereof,

wherein each of the plurality of carrier polymer-agent components comprises an elongate member comprising a proximal end, a distal end, and an outer surface therebetween;

wherein the proximal end of each elongate member is attached to the elastomer component and projects radially from the elastomer component, each elongate member having its distal end not attached to the elastomer component and located at a larger radial distance from the elastomer component than the proximal end;

wherein the elastomer is attached directly or indirectly to each elongate member by an intercomponent anchor;

wherein the gastric residence system is configured to have a compacted form in a container, suitable for administration orally or through a feeding tube; and an uncompacted form when released from the container in the stomach of the patient;

wherein the gastric residence system is retained in the stomach for a period of at least about 24 hours; and

wherein the system releases a therapeutically effective amount of therapeutic agent over at least a portion of the period in which the system is retained in the stomach.

14. The gastric residence system of claim 13, wherein a first portion of each intercomponent anchor is located within the elastomer, and a second portion of each intercomponent anchor is located within:

a) a corresponding first segment of interfacing polymer, wherein each corresponding first segment of interfacing polymer is also attached directly or indirectly to a corresponding one of the elongate members;

b) a corresponding segment of linker, wherein each corresponding segment of linker is also attached directly or indirectly to a corresponding one of the elongate members; or

c) a corresponding one of the elongate members.

15. The gastric residence system of claim 13, wherein:
a first portion of each intercomponent anchor is located within the elastomer, and
a second portion of each intercomponent anchor is located within a corresponding first segment of interfacing polymer,
wherein each corresponding first segment of interfacing polymer is also attached to a corresponding linker, and
each corresponding linker is attached to a corresponding one of the elongate members.

16. The gastric residence system of claim 13, wherein:
a first portion of each intercomponent anchor is located within the elastomer, and
a second portion of each intercomponent anchor is located within a corresponding first segment of interfacing polymer,
wherein each corresponding first segment of interfacing polymer is also attached to a corresponding linker,
wherein each corresponding linker is attached to a corresponding second segment of interfacing polymer; and
each corresponding second segment of interfacing polymer is attached to a corresponding one of the elongate members.

17. The gastric residence system of any one of claims 13-16, wherein the elastomer is overmolded over the first portions of the intercomponent anchors.

18. The gastric residence system of any one of claims 14-17, wherein the first segment of each interfacing polymer, linker, or elongate member is overmolded over the corresponding second portion of the intercomponent anchors.

19. A method of making an elastomer-intercomponent anchor assembly comprising:
overmolding an elastomer component over a first portion of a plurality of at least three intercomponent anchors.

20. A method of making an elastomer-intercomponent anchor-interfacing polymer assembly comprising:
overmolding each one of a plurality of interfacing polymer components over a second portion of a corresponding one of the at least three intercomponent anchors of the elastomer-intercomponent anchor assembly of claim 19.

21. An elastomer-intercomponent anchor assembly comprising:
a plurality of intercomponent anchors comprising a first portion and a second portion; and
an elastomer;
wherein the elastomer covers the first portion of the plurality of intercomponent anchors.

22. An elastomer-intercomponent anchor-interfacing polymer assembly comprising:
a plurality of interfacing polymer components covering the second portion of a corresponding one of the at least three intercomponent anchors of the elastomer-intercomponent anchor assembly of claim 21.

23. A method of making a gastric residence system assembly comprising:
a) overmolding an elastomer component over a first portion of a plurality of at least three intercomponent anchors; and
b) overmolding a plurality of interfacing polymer components over a second portion of each intercomponent anchor, wherein each interfacing polymer component is overmolded over a corresponding one of the at least three intercomponent anchors.

24. A gastric residence system for administration to the stomach of a patient, comprising: an elastomer component, wherein the elastomer is bi-concave or concavo-convex; a plurality of at least three carrier polymer-agent components comprising a carrier polymer and a therapeutic agent or a salt thereof, wherein each of the plurality of carrier polymer-agent components is an elongate member comprising a proximal end, a distal end, and an outer surface therebetween; wherein the proximal end of each elongate member is attached to the elastomer component and projects radially from the elastomer component, each elongate member having its distal end not attached to the elastomer component and located at a larger radial distance from the elastomer component than the proximal end; wherein the gastric residence system is configured to have a

compacted form in a container, suitable for administration orally or through a feeding tube; and an uncompacted form when released from the container in the stomach of the patient; wherein the gastric residence system is retained in the stomach for a period of at least about 24 hours; and wherein the system releases a therapeutically effective amount of therapeutic agent over at least a portion of the period in which the system is retained in the stomach.