A GASTRIC RESIDENCE ARTICLE FOR ORAL ADMINISTRATION

FIELD OF INVENTION

[0001] The present invention relates to a gastric residence article for oral administration.

BACKGROUND

[0002] Medical adherence to drug regimens over an extended duration is often poor. Low adherence rates are highest in primary and secondary prevention when the disease to be prevented or treated is often asymptomatic, and the drug regimens have no immediate tangible effects. Current approaches to improving adherence rates, such as educational interventions and counseling, have only achieved modest improvements.

[0003] Pharmacologic solutions, such as invasive delivery methods and pharmacologic agents, are often less well received due their invasive nature. In contrast, oral administration of a pharmaceutical drug is more widely accepted as it is easier and less expensive. However, the transit time through the human gastrointestinal tract is typically only about 24 to 48 hours, including approximately 1 to 2 hours in the stomach, approximately 3 hours in the small intestine, and approximately 6 to 13 hours in the large intestine. Therefore, a single administration of the drug usually cannot achieve the prescribed dosage frequency over a duration longer than the transit time.

[0004] One approach to achieving the desired dosage frequency over an extended duration with oral-administered dosage forms is by attaching the dosage form to a shape memory part to form a gastric retention device. The shape memory material needs to have a minimum flexural modulus to resist being pushed through the pyloric sphincter that connects the stomach to the duodenum, thereby preventing the dosage form from exiting the gastric chamber.

[0005] However, the conventional gastric retention devices have numerous drawbacks. The dosage form is typically attached to the shape memory part using a fusing agent, but the limited surface area available for the fusing agent to adhere to leads to insufficient adherence strength. As a result, the dosage form can easily become detached from the shape memory part and may not be retained in the gastric chamber.

[0006] Additionally, it is challenging to control the dissolution rate of dosage forms over time. Dosage forms typically dissolve uniformly from all exposed surfaces, resulting in an initial surge in the dissolution rate due to the relatively large surface area. As the surface area of the dosage forms decrease, the dissolution rate gradually declines. This inconsistency in the absorption of the dosage forms by the stomach is not ideal as it affects the efficacy of the dosage forms.

[0007] A need therefore exists to address at least one of the problems above or to provide a useful alternative.

SUMMARY

[0008] According to a first aspect of the present invention, there is provided a gastric residence article for oral administration comprising:

a foldable central superelastic alloy component comprising a plurality of ribs, wherein the foldable central superelastic alloy component undergoes elastic deformation when the gastric residence article is in a folded configuration and recoils when the gastric residence article assumes an expanded configuration;

a plurality of linker components radially connected to the foldable central superelastic alloy component, each linker component comprising a first side and a second side opposite the first side, and the first side of each linker component being individually connected to a corresponding rib; and

a plurality of elongated limb components comprising a core shaft and an outer layer encapsulating the core shaft, wherein each elongated limb component is individually connected to the second side of a corresponding linker component,

wherein the plurality of linker components is configured to be structurally compromised in the expanded configuration in-vivo, thereby resulting in a loss of a shape of the gastric residence article,

wherein the core shaft has an active substance, and the outer layer has a lower concentration of the active substance than the core shaft, and

wherein each elongated limb component comprises at least one slit formed on an exterior surface of the outer layer, the at least one slit extending across at least 50% of a length of the elongated limb component.

[0009] The at least one slit may extend to a depth of 50% or more of a thickness of the outer layer.

[0010] The at least one slit may have a width of 2 millimeter or less.

[0011] A ratio of cross-sectional areas of the core shaft to the outer layer may be between 1 to 10.

[0012] The outer layer may be devoid of the active substance.

[0013] The active substance may be a therapeutic agent or a diagnostic agent.

[0014] Each elongated limb component may further comprise one or more spacers located along the length of the elongated limb component.

[0015] The plurality of linker components may be configured to be structurally compromised in the expanded configuration in-vivo by degrading, dissolving, disassociating, or mechanically weakens.

[0016] Less than 35% of the active substance may be released within 20% of an effective release period, and more than 80% of the active substance may be released within 90% of the effective release period.

[0017] According to a second aspect of the present invention, there is provided a gastric residence article for oral administration comprising:

a foldable central superelastic alloy component comprising a plurality of ribs, wherein the foldable central superelastic alloy component undergoes elastic deformation when the gastric residence article is in a folded configuration and recoils when the gastric residence article assumes an expanded configuration;

a plurality of linker components radially connected to the foldable central superelastic alloy component, each linker component comprising a first side and a second side opposite the first side, and the first side of each linker component being individually connected to a corresponding rib; and

a plurality of elongated limb components comprising a core shaft and an outer layer encapsulating the core shaft, wherein each elongated limb component is individually connected to the second side of a corresponding linker component,

wherein the plurality of linker components is configured to be structurally compromised in the expanded configuration in-vivo, thereby resulting in a loss of a shape of the gastric residence article,

wherein the core shaft has an active substance, and the outer layer has a lower concentration of the active substance than the core shaft, and

wherein the outer layer has at least one thinned region, the at least one thinned region occupying 0.5% to 20% of an exterior surface of the outer layer.

[0018] The at least one thinned region may have a thickness of less than 0.2 millimeter.

[0019] The at least one thinned region may extend to a depth of 70% or more of a thickness of the outer layer.

[0020] The thinned region may be formed using at least one process selected from a group consisting of: heat deformation, surface cutting, and laser vaporization.

[0021] A ratio of cross-sectional areas of the core shaft to the outer layer may be between 1 to 10.

[0022] The outer layer may be devoid of the active substance.

[0023] The active substance may be a therapeutic agent or a diagnostic agent.

[0024] Each elongated limb component may further comprise one or more spacers located along the length of the elongated limb component.

[0025] The plurality of linker components may be configured to be structurally compromised in the expanded configuration in-vivo by degrading, dissolving, disassociating, or mechanically weakens.

[0026] Less than 35% of the active substance may be released within 20% of an effective release period, and more than 80% of the active substance may be released within 90% of the effective release period.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] Embodiments of the invention are provided by way of example only, and will be better understood and readily apparent to one of ordinary skill in the art from the following written description and the drawings, in which:

[0028] Figure 1A illustrates a schematic diagram showing a gastric residence article in an expanded configuration in accordance with an example embodiment.

[0029] Figure 1B illustrates a transparent section view of the gastric residence article of Figure 1A.

[0030] Figure 1C illustrates a schematic diagram showing the gastric residence article of Figure 1A in a folded configuration.

[0031] Figure 1D illustrates a schematic diagram showing another expanded configuration of the gastric residence article in Figure 1A in-vivo.

[0032] Figure 1E illustrates a transparent section view of the gastric residence article 100 of Figure 1D.

[0033] Figure 2A illustrates an end of a rib of a gastric residence article in accordance with an example embodiment.

[0034] Figure 2B illustrates a first example of a shaped end of Figure 1B.

[0035] Figure 2C illustrates a second example of a shaped end of Figure 1B.

[0036] Figure 2D illustrates a third example of a shaped end of Figure 1B.

[0037] Figure 2E illustrates a fourth example of a shaped end of Figure 1B.

[0038] Figure 3A illustrates an enlarged view of the distal region of Figures 1A, 1B and 1C.

[0039] Figure 3B illustrates an enlarged view showing the interlocking connection between the distal region and the linker component of Figures 1A, 1B and 1C.

[0040] Figure 4 illustrates a bar chart showing the retention times for two gastric residence articles in the gastric chamber of Labrador dogs.

[0041] Figure 5 illustrates a schematic diagram showing a gastric residence article in an expanded configuration in accordance with another example embodiment.

[0042] Figure 6 illustrates an enlarged view of a partial assembly of the elongated limb component of Figure 5.

[0043] Figure 7A illustrates a cross-sectional view of an elongated limb component having thinned regions in accordance with an example embodiment.

[0044] Figure 7B illustrates a cross-sectional view of another elongated limb component having at least one thinned region in accordance with an example embodiment.

[0045] Figure 8 illustrates a line chart showing dissolution rates of Risperidone for six gastric residence articles in simulated gastric fluid over a period of time.

DETAILED DESCRIPTION

[0046] Figure 1A illustrates a schematic diagram showing a gastric residence article 100 in an expanded configuration in accordance with an example embodiment. Figure 1B illustrates a transparent section view of the gastric residence article 100 of Figure 1A.

[0047] The gastric residence article 100 includes an outer portion 102 having a central region 104. The central region 104 is made of at least one material selected from a group consisting of polyvinyl chloride, synthetic rubber, neoprene, nylon, PVB, silicone, acrylonitrile butadiene styrene, polyethylene terephthalate, polybutylene terephthalate, and polyurethane. The outer portion 102 further includes a plurality of distal regions 106 radially connected to the central region 104. The plurality of distal regions 106 is made of at least one material selected from a group consisting of polypropylene, polystyrene, polyvinyl chloride, synthetic rubber, phenol formaldehyde resin (or Bakelite), neoprene, nylon, polyacrylonitrile, PVB, silicone, acrylonitrile butadiene styrene, high density polyethylene, polycarbonate, polycaprolactone, polylactic acid, acrylic, polyethylene terephthalate, polybutylene terephthalate, acetal, polyimide, polyurethane, and epoxy.

[0048] The gastric residence article 100 also includes a foldable central superelastic alloy component 108 made of at least one superelastic alloy. The foldable central superelastic alloy component 108 is securely received within the outer portion 102 and includes six ribs 110, each with an individual shaped end 112. Each shaped end 112 is individually embedded in a corresponding distal region 106 to form a secure fastening connection. As shown in Figure 1B, each shaped end 112 is a protrusion embedded in the distal region 106 to prevent movement

of the distal region 106 and to ensure alignment and stability of the distal region 106 with respect to the ribs 110.

[0049] The gastric residence article 100 further includes a plurality of linker components 114, which has a first side and a second side opposite the first side. The first side of each linker component 114 is individually connected to a corresponding distal region 106. As shown in Figure 1B, the first side of each linker component 114 has an indentation, and the corresponding distal region has a protrusion 116. These indentation and protrusion 116 form an interlocking connection. The plurality of linker components 114 is configured to be structurally compromised in the expanded configuration in-vivo, resulting in a loss of a shape of the gastric residence article 100.For example, the linker components 114 include a material that undergoes hydrolysis and/or water absorption in a gastric environment, leading to degradation, dissolution, disassociation, or mechanically weakening. As a result, the gastric residence article 100 loses its shape and passes through the gastric cavity of a patient.

[0050] Additionally, the gastric residence article 100 includes a plurality of elongated limb components 118. Each elongated limb component 118 is individually connected to the second side of a corresponding linker component 114. At least one of the elongated limb components 118 has an active substance, such as a therapeutic agent or a diagnostic agent, for delivering gastroretentive drug at a predetermined rate.

[0051] Figure 1C illustrates a schematic diagram showing the gastric residence article 100 of Figure 1A in a folded configuration. The foldable central superelastic alloy component 108 undergoes elastic deformation when the gastric residence article 100 is in a folded configuration, as shown in Figure 1C. At this folded configuration, the corresponding distal regions 106, linker components 114, and elongated limb components 116 form triangular prisms that can fit tightly together, allowing for easy storage and oral administration.

[0052] Figure 1D illustrates a schematic diagram showing another expanded configuration of the gastric residence article 100 in Figure 1A in-vivo. Figure 1E illustrates a transparent section view of the gastric residence article 100 of Figure 1D. When the medication is taken, a patient swallows the gastric residence article 100, and the gastric residence article 100 assumes an expanded configuration in-vivo, as the foldable central superelastic alloy component 108 recoils in the gastric cavity.

[0053] The expanded configuration of the gastric residence article 100 allows retention of the gastric residence article 100 in a patient's gastric cavity for an extended duration, e.g. 24 hours or more. The gastric residence article 100 resists bending in-vivo due to the the peristatic waves of the stomach compressing the article 100, as shown in Figures 1D and 1E. After a certain period in the gastric environment, the linker components 114 become structurally compromised. This process makes the linker components 114 flexible or causes them to break apart, allowing for bending or disconnection of the elongated limb components 118 with respect to the outer portion 102. As a result, the gastric residence article 100 loses its shape and passes through the gastric cavity of a patient.

[0054] In an embodiment, the plurality of distal regions 106 has a higher level of hardness compared to the central region 104. Increasing the hardness of the distal region limits the movement of the elongated limb component 118 relative to the outer portion 102, thereby enhancing the ability of the gastric residence article 100 to be retained in the gastric cavity. Additionally, the plurality of distal regions 106 can have a hardness level of 50D or more on the shore hardness scale. The central region 104 has a relatively lower hardness to avoid impeding the folding of the gastric residence article 100.Without the distal regions 106, the low hardness level of the central region 104 may cause the outer portion 102 to deform, resulting in significant bending of the elongated limb component 118 in-vivo relative to the foldable central superelastic alloy component 108. Consequently, the gastric residence article 100 will lose its shape and discharge from the gastric cavity prematurely. In the claimed invention, , the distal regions 106 has a relatively higher hardness level than the central region 104 to form a secure fastening connection with the ribs 110 of the foldable central superelastic alloy component 108. Therefore, when the gastric residence article 100 is in the expanded configuration, the elongated limb components 118 will not bend relative to the foldable central superelastic alloy component 108 due to the deformation of the central region 104, preventing the gastric residence article 100 from passing through the gastric cavity prematurely.

[0055] In an embodiment, the gastric residence article 100 has an opening diameter of at least 2 cm and a folding force of at least 0.5 N in the expanded configuration.

[0056] In the embodiment described in Figures 1A-1E, the foldable central superelastic alloy component 108 includes six ribs 110, each with an individual shaped end 112 individually embedded in a corresponding distal region 106 to form a secure fastening connection. In an alternate embodiment, the ribs 110 may not include a shaped end. Instead, the foldable central

superelastic alloy component 108 may simply include a plurality of ribs 110, and each rib has an end that is individually embedded into the corresponding distal region 106.

[0057] In an alternate embodiment, the gastric residence article 100 further includes a casing that houses the entire assembly, enabling easy storage and oral administration. When the medication is taken, the casing will degrade, dissolve, disassociate, or mechanically weaken in vivo, and the gastric residence article 100 assumes an expanded configuration as the foldable central superelastic alloy component 108 recoils in the gastric environment.

[0058] In an embodiment, the foldable central superelastic alloy component 108 includes at least one superelastic alloy selected from a group consisting of Nitinol (Ni-Ti), Brass (Cu–Zn), copper-aluminium-nickel (Cu–Al–Ni) alloy, gold-cadmium (Au–Cd) alloy, gold-copper-zinc (Au-Cu-Zn) alloy, indium–thallium (In–Tl) alloy, cobalt-nickel-aluminium (Co-Ni-Al) alloy, cobalt-nickel-gallium (Co-Ni-Ga) alloy, copper-aluminium-beryllium-zirconium (Cu-Al-Be-Zr), copper-aluminium-beryllium-chromium (Cu-Al-Be-Cr) alloy, copper-aluminium-beryllium-gadolinium (Cu-Al-Be-Gd) alloy, copper-aluminium-nickel-hafnium (Cu-Al-Ni-Hf) alloy, copper-tin (Cu-Sn) alloy, copper-zinc-silicon (Cu-Zn-Si) alloy, copper-zinc-aluminium (Cu-Zn-Al) alloy, copper-zinc-silicon (Cu-Zn-Sn) alloy, iron-manganese-silicon (Fe-Mn-Si) alloy, iron-platinum (Fe-Pt) alloy, manganese-copper (Mn-Cu) alloy, nickel-iron-gallium (Ni-Fe-Ga) alloy, (Ni-Ti-Hf) alloy, nickel-titanium-palladium (Ni-Ti-Pd) alloy, nickel-manganese-gallium (Ni-Mn-Ga) alloy, nickel-manganese-gallium-copper (Ni-Mn-Ga-Cu) alloy, nickel-manganese-gallium-cobalt (Ni-Mn-Ga-Co) alloy, titanium-niobium (Ti-Nb) alloy.

[0059] In another embodiment, the foldable central superelastic alloy component 108 can also be made of a shape memory alloy selected from a group consisting of Ni-Ti, Ni-Ti-Hf, Ni-Ti-Pd, Ni-Fe-Ga, Ni-Mn-Ga, Ni-Mn-Ga-Cu, Ni-Mn-Ga-Co, Ag-Cd, Co-Ni-Al, Co-Ni-Ga, Cu-Al-Be-X (X: Zr, B, Cr, Gd), Cu-Al-Ni, Cu-Al-Ni-Hf, Cu-Sn, Cu-Zn, Cu-Zn-X (X = Si, Al, Sn), Fe-Mn-Si, Fe-Pt, Mn-Cu, Ti-N.

[0060] Shape memory alloys belong to the family of superelastic alloys. A suitable shape memory alloy for the foldable central superelastic alloy component 108 has an austenite transformation finish temperature (Af) slightly below normal body temperature. At temperatures below the Af (e.g. 30°C), shape memory alloys are in martensite phase and can be malleable. However, when the shape memory alloys are heated to a temperature above the Af, they become superelastic and will revert to their initial unfolded state. During production and storage, the shape memory alloys are in the martensite phase and thus, the gastric

residence article 100 can retain its folded configuration without a restraining structure, such as the casing described above. Following oral administration of the gastric residence article 100, the temperature of the shape memory alloy increases due to the natural heat of a human's body. This causes the shape memory alloy to go through the transformation from martensite phase to austenite phase, thereby allowing retention of the gastric residence article 100 in the gastric cavity.

[0061] Figure 2A illustrates an end of a rib 200 of a gastric residence article in accordance with an example embodiment. As shown in Figure 2A, the rib 200 extends into the distal region 201 of the gastric residence article and is embedded in it. The rib 200 does not include a shaped end. As the ribs 200 are embedded in the distal regions 201 with an enhanced hardness level, the resistance of the elongated limb component to bend in-vivo due to the deformation of the central region significantly increases.

[0062] Figures 2B-2E illustrate examples of shaped ends 112 of Figures 1B. In Figure 2B, the shaped end 112 includes a beam 202 embedded in the distal region 106. The beam 202 consists of a vertical web with a horizontal flange at the end, resembling the letter "T", to create a secure fastening connection with the corresponding distal region 106.

[0063] In Figure 2C, the shaped end 112 includes a hook 204 embedded in the distal region 106. The hook 204 has a straight body with a bent shape extending at a right angle, resembling the letter "J", for latching on the corresponding distal region 106 to form a secure fastening connection. In an alternate embodiment, the shaped end 112 can include a bend formed at any internal bending angle θ of 135 degrees or less.

[0064] In Figure 2D, the shaped end 112 includes spiraling patterns 206 embedded in the distal region 106. The spiraling patterns 206 consists of spirals or helical shapes to form a secure fastening connection with the corresponding distal region 106. In Figure 2E, the shaped end 112 includes a recessed shape 208 embedded in the distal region 106. The recessed shape 208 enables the shaped end 112 to firmly hold the distal region 106 and prevent detachment.

[0065] In alternate embodiments, the shaped ends 112 can include other features, such as threads, a stud, a flange, and a protrusion, which enable them to form secure fastening connection with the distal regions 106. When a polymer is molded to the shaped ends 112 to

form the distal regions 106, these features engage and anchor the distal regions 106, preventing any movement of the distal regions 106.

[0066] Figure 3A illustrates an enlarged view of the distal region 106 of Figures 1A, 1B and 1C. As shown Figure 3A, the distal region 106 has a protrusion 116 in the shape of a wedge at its outward facing side. The protrusion 116 is configured to individually form an interlocking connection with the first side of the linker component 114.

[0067] Figure 3B illustrates an enlarged view showing the interlocking connection between the distal region 106 and the linker component 114 of Figures 1A, 1B and 1C. The interlocking connection consists of the protrusion 116 on the outward facing side of the distal region 106 and a corresponding indentation on the first side of the linker component 114. When joined together, the protrusion 116 fits snugly into the indentation, creating a secure and stable connection, preventing unintended detachment of the linker component 114 from the distal region 106.

[0068] In an alternate embodiment, instead of a protrusion on the distal region 106 and a corresponding indentation on the linker component 114, the interlocking connection can be formed by a protrusion on the linker component 114 and a corresponding indentation on the distal region 106. In alternate embodiments, the interlocking connection can also be formed by other types of joints, such as adhesive joint, ball and socket joint, finger joint.

[0069] Figure 4 illustrates a bar chart 402 showing the retention times for two gastric residence articles in the gastric chamber of Labrador dogs. The gastric residence articles correspond to article 3 and 5 from Example 2 below. The vertical axis represents the retention time scale, marked in days. The horizontal axis represents the two articles. The first bar 404 represents a first gastric residence device (Article 3 in Example 2) that does not have ribs with shaped ends for forming a fastening connection between the foldable central superelastic alloy component and the distal regions. The second bar 406 represents a second gastric residence device (Article 5 in Example 2) with the foldable central superelastic alloy component having ribs with shaped ends to form fastening connections with the corresponding distal regions, in accordance with an example embodiment. As depicted in Figure 4, the retention time of the first gastric residence device is slightly less than 2 days, while the retention time of the second gastric residence device is significantly longer at approximately 11 days. This visual representation clearly demonstrates the substantial increase in retention time for having the

fastening connections between the foldable central superelastic alloy component and the distal regions.

[0070] Figure 5 illustrates a schematic diagram showing a gastric residence article 500 in an expanded configuration in accordance with another example embodiment. The gastric residence article 500 includes an outer portion 502 having a central region 504 and a plurality of distal regions 506 radially connected to the central region 504. The gastric residence article 500 also includes a foldable central superelastic alloy component made of at least one superelastic alloy. The superelastic alloy component is securely received within the outer portion 502 and includes a plurality of ribs.

[0071] The gastric residence article 500 further includes a plurality of linker components 508, which has a first side and a second side opposite the first side. The first side of each linker component 508 is individually connected to a corresponding distal region 506 to form an interlocking connection. The plurality of linker components 508 is configured to be structurally compromised in the expanded configuration in-vivo, resulting the gastric residence article 500 losing its shape. For example, the linker components 508 include a material that undergoes hydrolysis and/or water absorption in a gastric environment, leading to degradation, dissolution, disassociation, or mechanically weakening. As a result, the gastric residence article 500 loses its shape and passes through the gastric cavity of a patient.

[0072] Additionally, the gastric residence article 500 includes a plurality of elongated limb components 510. The plurality of elongated limb components 510 includes a core shaft and an outer layer encapsulating the core shaft. Each elongated limb component 510 is individually connected to the second side of a corresponding linker component 508. At least one of the elongated limb components 510 has an active substance, such as a therapeutic agent or a diagnostic agent, for delivering gastroretentive drug at a predetermined rate. Slits 512 are formed on an exterior surface of the outer layer along a length of the elongated limb components 510 to increase a dissolution rate of the active substance through the outer layer.

[0073] The elongated limb components 510 further includes spacers 514 individually located along the length of the elongated limb components 510 at distal ends of the components 510. The length of the core shaft is dependent on the drug dose required. The spacers 514 may allow the elongated limb components 510 to have the same length regardless of the drug dose. Other additions to the elongated limb components 510, such as fluorescence (e.g. barium

sulfate) or metal ball bearings, can also be implemented into the spacers 514, since they will not affect the dissolution rate of the active substance.

[0074] In an embodiment, the core shaft has an active substance, and the outer layer has a lower concentration of the active substance than the core shaft. The outer layer can also be devoid of the active substance.

[0075] In the embodiment explained in Figure 5, the gastric residence article 500 includes an outer portion 502 having a central region 504 and a distal region 506. In an alternate embodiment, the gastric residence article 500 can operate effectively even in the absence of the outer portion 502. In this alternate embodiment, the first side of each linker component 508 is individually connected to a corresponding rib.

[0076] In the embodiment explained in Figure 5, the spacers 514 are individually located at the distal end of the elongated limb components 510. In an alternate embodiment, the spacers 514 can be located anywhere along the length of the elongated limb components 510, e.g. at the proximal ends of the components 510 adjacent the linker components 508. Additionally, each elongated limb component 510 may have more than one spacer.

[0077] Figure 6 illustrates an enlarged view of a partial assembly of the elongated limb component 510 of Figure 5. The elongated limb component 510 includes a core shaft 602 and an outer layer 604 encapsulating the core shaft 510. Slits 606 are formed on an exterior surface of the outer layer 604 along an entire length of the elongated limb component 510. The slits 606 can be formed using at least one process selected from a group consisting of: laser vaporization, surface cutting, heat deformation, and co-extrusion. For the co-extrusion process, a co-extruder having a modified die head creates the slit using a protrusion.

[0078] In an alternate embodiment, the slits 606 extend across at least 50% of the length of the elongated limb component 510. Additionally, the slits 606 can extend to a depth of 50% or more of a thickness of the outer layer 604 and have a width of 2 millimeter or less. Further, a ratio of cross-sectional areas of the core shaft 602 to the outer layer 604 is between 1 to 10.

[0079] Figure 7A illustrates a cross-sectional view of an elongated limb component 702 having thinned regions 704 in accordance with an example embodiment. The elongated limb component 702 includes a core shaft 706 and an outer layer 708 encapsulating the core shaft 706.

[0080] Figure 7B illustrates a cross-sectional view of another elongated limb component 710 having at least one thinned region 712 in accordance with an example embodiment. The elongated limb component 710 includes a core shaft 714 and an outer layer 716 encapsulating the core shaft 714.

[0081] The thinned regions 704, 712 can increase the dissolution rate of the active substance through the outer layer 708, 716. Additionally, the at least one thinned region 704, 712 can extend to a depth of 50% or more of the thickness of the outer layer 708, 716. The at least one thinned region 704, 712 can have a thickness of less than 0.2 millimeter and occupy 0.5% to 20% of an exterior surface of the outer layer 708, 716. The thinned region 704, 712 is defined as any part of the outer layer 708, 716 whereby the shortest distance from the outer surface of the outer layer 708, 716 to the surface of the core shaft is less than 50% of the average thickness of the outer layer or less than 0.2 millimeter. The thinned region can be formed during the production process whereby the inner and outer layers are joined or can be formed using at least one process selected from a group consisting of: heat deformation, surface cutting, and laser vaporization.

[0082] For a conventional oral-administered drug, the drug is released uniformly from all exposed surfaces, and this results in a dissolution profile which has a faster dissolution rate at the start and a slower dissolution rate towards the end. This is because only the drug from the surface can be released. Initially, the drug is already at the surface and can be released quickly, but as the dissolution progresses, the drug has to diffuse through a longer distance to reach the surface to be released. This causes the dissolution rate of the drug to slow down. Using a coating with a controlled diffusion rate is a common method used to better control the dissolution profile. However, the ability of the coating is limited since the mechanism for drug release is still the same as the dissolution will still gradually slow down as the drug needs to diffuse through a longer distance to the surface to be released as more drug is released. Thus, it is challenging to achieve a good dissolution curve throughout the effective release period, which is the duration for a complete release of an active substance.

[0083] In the embodiments in Figures 6, 7A, and 7B, by applying the outer layer 604, 708, 716 on the core shaft 602, 706, 714, the permeability of the outer layer 604 708, 716 can be selectively modified at selective areas to reduce the distance between the core shaft 602, 706, 714 and the exterior surface of the outer layer 604, 708, 716. This can be done by either reducing the thickness of the outer layer or forming a slit to completely expose the core shaft 602, thereby increasing the dissolution rate of the active substance. This may advantageously

achieve a more controlled dissolution rate by forming slits 606 or thinned regions 704, 712 of various dimensions on the outer layer 604, 708, 716, as well as by changing the compositions of the outer layer 604, 708, 716, to obtain the desired dissolution rates of the active substance by controlling the locations and rates at which the active substance is released from the surface. Advantageously, in these embodiments, less than about 35% of the active substance can be released within about 20% of the effective release period, and more than about 80% of the active substance can be released within about 90% of the effective release period.

[0084] Figure 8 illustrates a line chart 802 showing dissolution rates of Risperidone for six gastric residence articles in simulated gastric fluid over a period of time. The horizontal axis represents the number of days, while the vertical axis represents the dissolution percentage of Risperidone in the simulated gastric fluid. The chart consists of six lines.

[0085] The first line 804, representing a gastric residence article with no outer layer, demonstrates an inconsistent dissolution rate of the Risperidone. At the beginning, the first line 804 has a steeper gradient, indicating a higher dissolution rate. However, as time progresses, the gradient of the first line 804 decreases, suggesting a reduction in the dissolution rate. In other words, the dissolution rate observed varies over the given timeframe.

[0086] The second line 806, third line 808, and fourth line 810, represents gastric residence articles with slits which propagate through 100%, 75%, 50% of the length of the elongated limb components respectively, in accordance with an example embodiment. The second line 806, third line 808, and fourth line 810 maintain uniform gradients, with less than about 35% of Risperidone being released within about 20% of the effective release period and more than about 80% of the Risperidone being released within about 90% of the effective release period. The line charts indicates that these gastric residence articles have a stable dissolution rate, and that nearly all the active substance is released at the end of the seven-day experiment. This emphasizes the consistent dissolution of the active substance attributed to the slits formed on the elongated limb components. The fifth line 812 represents another gastric residence article with slits which propagate through 40% of the length of its elongated limb components. The fifth line 812 maintains a uniform gradient, but the release of the Risperidone is slower as compared to the preceding gastric residence articles.

[0087] The sixth line 814 represents a gastric residence article having an outer layer with no slits. Due to a lack of slits on the elongated limb components, the gastric residence article maintains a slow release of the Risperidone throughout the effective release period.

EXAMPLE 1

[0088] An example of the process to produce the gastric residence article 100 described in Figures 1A, 1B and 1C is provided below.

[0089] 0.35 mm thick Nitinol plates are stamped to obtain the foldable central superelastic alloy component 108. The central region 104 and distal regions 106 of the outer portion 102 are formed by injecting PC-3575A and PC-3572D from Lubrizol respectively.

[0090] 99g of HPMC-AS-HG from Shin-Etsu, 99g of PCL, and 2g of silica are blended until the mixture is homogenous. The homogenous powder is then loaded into the feeder of a Pharma 11 Twin-Screw Extruder from Thermo Scientific with a customized triangular die head to form a triangular filament which is cut into 3mm segments to form the linker components 114.

[0091] 130g of PCL powder, 40g of Evonik eudragit RL PO powder, 28g of the active ingredient in the powdered state, and 2g of silica powder are blended until the mixture is homogenous. The homogenous powder is then loaded into the feeder of a Pharma 11 Twin-Screw Extruder from Thermo Scientific with a customized triangular die head to form a triangular filament which is then cut to 8mm segments to form the elongated limb component 118.

[0092] The outer portion 102, foldable central superelastic alloy component 108, linker components 114 and elongated limb components 118 are then loaded into a customized mold and heat fused together via a laser to form the gastric residence article 100.

EXAMPLE 2

[0093] An experiment using six gastric residence articles is described below.

[0094] Six gastric residence articles were made using different materials for the outer portion and the foldable central superelastic alloy component, as shown in the table below. The same linker components and elongated limb components were used for all six articles which were produced using the same parameters. The gastric residence articles were then loaded into size 0 capsules.

[0095] The capsules containing the gastric articles were then fed to Labradors on different occasions. X-ray of the abdomen were conducted every day and the retention periods in the abdomen, marked in days, were recorded as below.

	1	2	3	4	5	6
Material for the foldable central superelastic alloy component	Nitinol	Nitinol	Nitinol	Nitinol	Nitinol	Nitinol
Shaped ends	Straight	Straight	Straight	A beam with T-shaped	A beam with T-shaped	A beam with T-shaped
Material for the central region	PC-3575A	PC-3575A	PC-3575A	PC-3575A	PC-3575A	PC-3575A
Material for the distal region	Covestro 1350D	TT-2075D-B40	PC-3575A	Covestro 1350D	TT-2075D-B40	PC-3575A
Hardness for material for the central region	75 Shore A	75 Shore A	75 Shore A	75 Shore A	75 Shore A	75 Shore A
Hardness for material for the distal region	50 Shore D	75 Shore D	75 Shore A	50 Shore D	75 Shore D	75 Shore A
Retention period (days)	7.3±1.5	7.8±1.7	1.8±0.7	9.3±3.2	11.3±3.3	2.6±0.3

EXAMPLE 3

[0096] An example of the process to produce a partial assembly the elongated limb component 510 shown in Figure 6 is provided below.

[0097] 110g of PCL powder, 50g of Evonik eudragit RL PO powder, 38g of the active ingredient in the powdered state, and 2g of silica powder are blended until the mixture is homogenous. The homogenous powder is then loaded into the feeder of a Pharma 11 Twin-Screw Extruder from Thermo Scientific. The extruded filament is then palletized to form the pallets for the core shaft 602.

[0098] 140g of PCL powder, 58g of Evonik eudragit RS PO powder, and 2g of silica powder are blended until the mixture is homogenous. The homogenous powder is then loaded into the feeder of a Pharma 11 Twin-Screw Extruder from Thermo Scientific. The extruded filament is then palletized to form the pallets for the outer layer 604.

[0099] The pallets of the core shaft 602 and outer layer 604 are fed into a co-extruder and extruded with a screw speed of 21rpm for the core shaft 602 and 9rpm for the outer layer 604. The extrusion head of the co-extruder is customized such that during extrusion, the outer layer 604 wrap around the core shaft 602. The die head is also customized so that the elongated limb component is triangular in shape, and the slits 606 are formed. The co-extruded filament is then cut to 6mm to form the elongated limb component.

EXAMPLE 4

[0100] Another example of the process to produce the elongated limb component 510 shown in Figure 5 is provided below.

[0101] 90g of PCL powder, 30g of Evonik eudragit RL PO powder, 30g of poloxmer 407 power, 48g of the active ingredient in the powdered state, and 2g of silica powder are blended until the mixture is homogenous. The homogenous powder is then loaded into the feeder of a Pharma 11 Twin-Screw Extruder from Thermo Scientific. The extruded filament is then palletized to form the pallets for the core shaft.

[0102] 170g of PCL powder, 28g of Evonik eudragit RS PO powder, and 2g of silica powder are blended until the mixture is homogenous. The homogenous powder is then loaded into the feeder of a Pharma 11 Twin-Screw Extruder from Thermo Scientific. The extruded filament is then palletized to form the pallets for the outer layer.

[0103] The pallets of the core shaft and outer layer are fed into a co-extruder and extruded with a screw speed of 18rpm for the core shaft and 12rpm for the outer layer. The extrusion head of the co-extruder is customized such that during extrusion, the outer layer will wrap around the core shaft. The die head is also customized so that the elongated limb component is triangular in shape and the slits are formed during the extrusion. The co-extruded filament is then cut to 6mm to form the assembly of the core shaft and outer layer.

[0104] 198g of PCL powder, and 2g of silica are blended until the mixture is homogenous. The homogenous powder is then loaded into the feeder of a Pharma 11 Twin-Screw Extruder from Thermo Scientific with a customized triangular die head to form a triangular filament which is then cut to 2mm segments to form a spacer. The spacers are then placed at an end of the assembly of the core shaft and outer layer using a heat fusing process to form the elongated limb component.

EXAMPLE 5

[0105] An example of the process to produce a spacer with barium sulfate.

[0106] 120g of PCL powder, 78g of barium sulfate powder, and 2g of silica powder are blended until the mixture is homogenous. The homogenous powder is then loaded into the feeder of a Pharma 11 Twin-Screw Extruder from Thermo Scientific with a customized triangular die head to form a triangular filament which is cut into 4mm segments to form the spacer components.

[0107] It will be appreciated by a person skilled in the art that numerous variations and/or modifications may be made to the present invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects to be illustrative and not restrictive.

CLAIMS

1. A gastric residence article for oral administration comprising:

a foldable central superelastic alloy component comprising a plurality of ribs, wherein the foldable central superelastic alloy component undergoes elastic deformation when the gastric residence article is in a folded configuration and recoils when the gastric residence article assumes an expanded configuration;

a plurality of linker components radially connected to the foldable central superelastic alloy component, each linker component comprising a first side and a second side opposite the first side, and the first side of each linker component being individually connected to a corresponding rib; and

a plurality of elongated limb components comprising a core shaft and an outer layer encapsulating the core shaft, wherein each elongated limb component is individually connected to the second side of a corresponding linker component,

wherein the plurality of linker components is configured to be structurally compromised in the expanded configuration in-vivo, thereby resulting in a loss of a shape of the gastric residence article,

wherein the core shaft has an active substance, and the outer layer has a lower concentration of the active substance than the core shaft, and

wherein each elongated limb component comprises at least one slit formed on an exterior surface of the outer layer, the at least one slit extending across at least 50% of a length of the elongated limb component.

2. The gastric residence article as claimed in claim 1, wherein the at least one slit extends to a depth of 50% or more of a thickness of the outer layer.

3. The gastric residence article as claimed in claim 1, wherein the at least one slit has a width of 2 millimeter or less.

4. The gastric residence article as claimed in claim 1, wherein a ratio of cross-sectional areas of the core shaft to the outer layer is between 1 to 10.

5. The gastric residence article as claimed in claim 1, wherein the outer layer is devoid of the active substance.

6. The gastric residence article as claimed in claim 1, wherein the active substance is a therapeutic agent or a diagnostic agent.

7. The gastric residence article as claimed in claim 1, wherein each elongated limb component further comprises one or more spacers located along the length of the elongated limb component.

8. The gastric residence article as claimed in claim 1, wherein the plurality of linker components is configured to be structurally compromised in the expanded configuration in-vivo by degrading, dissolving, disassociating, or mechanically weakens.

9. The gastric residence article as claimed in claim 1, wherein less than 35% of the active substance is released within 20% of an effective release period, and more than 80% of the active substance is released within 90% of the effective release period.

10. A gastric residence article for oral administration comprising:

a foldable central superelastic alloy component comprising a plurality of ribs, wherein the foldable central superelastic alloy component undergoes elastic deformation when the gastric residence article is in a folded configuration and recoils when the gastric residence article assumes an expanded configuration;

a plurality of linker components radially connected to the foldable central superelastic alloy component, each linker component comprising a first side and a second side opposite the first side, and the first side of each linker component being individually connected to a corresponding rib; and

a plurality of elongated limb components comprising a core shaft and an outer layer encapsulating the core shaft, wherein each elongated limb component is individually connected to the second side of a corresponding linker component,

wherein the plurality of linker components is configured to be structurally compromised in the expanded configuration in-vivo, thereby resulting in a loss of a shape of the gastric residence article,

wherein the core shaft has an active substance, and the outer layer has a lower concentration of the active substance than the core shaft, and

wherein the outer layer has at least one thinned region, the at least one thinned region occupying 0.5% to 20% of an exterior surface of the outer layer.

11. The gastric article as claimed in claim 10, wherein the at least one thinned region has a thickness of less than 0.2 millimeter.

12. The gastric article as claimed in claim 10, wherein the at least one thinned region extends to a depth of 70% or more of a thickness of the outer layer.

13. The gastric residence article as claimed in claim 10, wherein the thinned region is formed using at least one process selected from a group consisting of: heat deformation, surface cutting, and laser vaporization.

14. The gastric residence article as claimed in claim 10, wherein a ratio of cross-sectional areas of the core shaft to the outer layer is between 1 to 10.

15. The gastric residence article as claimed in claim 10, wherein the outer layer is devoid of the active substance.

16. The gastric residence article as claimed in claim 10, wherein the active substance is a therapeutic agent or a diagnostic agent.

17. The gastric residence article as claimed in claim 10, wherein each elongated limb component further comprises one or more spacers located along the length of the elongated limb component.

18. The gastric residence article as claimed in claim 10, wherein the plurality of linker components is configured to be structurally compromised in the expanded configuration in-vivo by degrading, dissolving, disassociating, or mechanically weakens.

19. The gastric residence article as claimed in claim 10, wherein less than 35% of the active substance is released within 20% of an effective release period, and more than 80% of the active substance is released within about 90% of the effective release period.