

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 to their invasive nature. In contrast, oral administration of a pharmaceutical drug is more widely accepted because 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 orally administered dosage forms is by attaching the dosage form to a shape memory part to create a gastric retention device. The shape memory material helps prevent the device from being pushed through the pyloric sphincter that connects the stomach to the duodenum, thereby preventing the dosage form from exiting the gastric chamber.

[0005] The conventional gastric retention devices have numerous drawbacks. The dosage form is typically attached to the shape memory part that is designed to be small for easy drug administration. However, due to the small size of the shape memory part, it may not have enough flexural strength to resist the external forces caused by peristaltic movements in the gastrointestinal tract. Often, the gastric retention device leaves the gastric chamber prematurely because the shape memory part lacks sufficient strength. This results in patients not receiving an adequate dosage of drugs.

[0006] A need therefore exists to address at least one of the problems above or to provide a useful alternative.

SUMMARY

[0007] According to an aspect of the present invention, there is provided a gastric residence article for oral administration comprising:

- an outer portion comprising a central region and a plurality of distal regions radially connected to the central region;

- a foldable central alloy component securely received within the outer portion, wherein the foldable central alloy component is configured to undergo elastic deformation when the gastric residence article is in a folded configuration and to recoil to allow for the gastric residence article to assume an expanded configuration;

- a plurality of linker components, 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 distal region; and

- a plurality of elongated limb components comprising an active substance, each elongated limb component being individually connected to the second side of a corresponding linker component, and the active substance being a therapeutic agent or a diagnostic agent,

- a plurality of flexible connectors connecting corresponding pairs of adjacent distal regions, wherein the flexible connectors are configured to fold when the gastric residence article is in the folded configuration and to unfold when the gastric residence article is in the expanded configuration, thereby applying force to resist a collapse of the gastric residence article in vivo,

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

[0008] When the gastric residence article is in the folded configuration, the plurality of flexible connectors may be folded such that all the flexible connectors are contained within gaps formed between the corresponding pairs of adjacent distal regions.

[0009] Each flexible connector may include a central peak that bends towards a central axis of the gastric residence article when the gastric residence article is in the folded configuration.

[0010] The plurality of distal regions may have a higher level of hardness than the central region.

[0011] The plurality of flexible connectors may be secured to the corresponding pair of adjacent distal regions.

[0012] The individual flexible connector may be formed in a structure selected from a group consisting of a wire, a tube, a ribbon, and a hollow disc.

[0013] The plurality of flexible connectors may be sequentially connected to form a unitary construction with two ends.

[0014] The two ends of the unitary construction may be connected to one distal region to form individual locking mechanisms for secure attachment.

[0015] The locking mechanisms may comprise the two ends forming individual hooks embedded in the one distal region.

[0016] The two ends of the unitary construction may form secure attachment with each other outside the plurality of distal regions.

[0017] Each of the flexible connectors may comprise two ends that form individual locking mechanism with the corresponding distal regions for secure attachment.

[0018] The plurality of flexible connectors may be made of an alloy.

[0019] The flexible connector may be made of at least one material selected from a group consisting of copper-aluminum-nickel alloys, nickel-titanium alloys, iron-based alloys, copper-based alloys.

[0020] The plurality of flexible connectors may form a unitary construction with the outer portion.

[0021] Each flexible connector may comprise an arc that forms a unitary construction with the outer portion.

[0022] The arc may have a hardness level of between 20 A and 50 D on the shore hardness scale.

[0023] The arc may have a Young's Modulus value of more than 15 MPa.

[0024] The arc may be 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.

[0025] Each flexible connector may comprise a membrane that forms a unitary construction with the outer portion.

[0026] The membrane may have a thickness of 0.3 - 0.8 mm.

[0027] The membrane may have a hardness level of not more than 50 D on the shore hardness scale.

[0028] The membrane may have a Young's Modulus value of more than 15 MPa.

[0029] The membrane may be 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] 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:

[0031] Figure 1A illustrates a schematic diagram showing a gastric residence article in an expanded configuration in accordance with an example embodiment.

[0032] Figure 1B illustrates a transparent view of the outer portion of the gastric residence article from Figure 1A, notably devoid of flexible connectors.

[0033] Figure 1C illustrates a perspective view of the gastric residence article of Figure 1A in a folded configuration.

[0034] Figure 1D illustrates a top view of the outer portion of the gastric residence article of Figure 1A in a folded configuration.

[0035] Figure 1E illustrates a top view of the gastric residence article shown in Figure 1A when it assumes a partially expanded configuration in vivo.

[0036] Figure 1F illustrates a side view of the gastric residence article of Figure 1E.

[0037] Figure 1G illustrates a transparent view of the outer portion of the gastric residence article depicted in Figure 1A.

[0038] Figure 2A illustrates a schematic diagram showing a gastric residence article in an expanded configuration in accordance with another example embodiment.

[0039] Figure 2B illustrates a schematic diagram showing a gastric residence article in an expanded configuration in accordance with a further example embodiment.

[0040] Figure 3 illustrates a schematic diagram showing a gastric residence article in an expanded configuration in accordance with another example embodiment.

DETAILED DESCRIPTION

[0041] 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 view of the outer portion of the gastric residence article 100 from Figure 1A, notably devoid of flexible connectors. 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.

[0042] 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.

[0043] The gastric residence article 100 also includes a foldable central alloy component 108 made of at least one alloy. The foldable central alloy component 108 is securely received within the outer portion 102 and includes six ribs 110 individually embedded in a corresponding distal region 106 to form a secure fit. This may advantageously prevent the movement of the distal regions 106 and to ensure alignment and stability of the distal regions 106 with respect to the corresponding ribs 110.

[0044] The gastric residence article 100 further includes a plurality of linker components 112. Each linker component 112 has a first side and a second side opposite the first side. The first sides of the linker components 112 are individually connected to their corresponding distal regions 106. The first side of each linker component 112 may have an indentation that connects to the corresponding protrusion of the corresponding distal region 106. The indentation and protrusion form an interlocking connection. The plurality of linker components 112 is configured to be structurally compromised in vivo, resulting in a loss of a shape of the gastric residence article 100. For example, the linker components 112 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.

[0045] Additionally, the gastric residence article 100 includes a plurality of elongated limb components 114. Each elongated limb component 114 is individually connected to the second side of a corresponding linker component 112. At least one of the elongated limb components 114 has an active substance, such as a therapeutic agent or a diagnostic agent, for delivering gastroretentive drug at a predetermined rate.

[0046] Furthermore, the gastric residence article 100 includes a plurality of flexible connectors 116 individually formed between each corresponding pair of adjacent distal regions 106. The flexible connectors 116 are in the form of a wire and are secured to the corresponding pair of

adjacent distal regions 106. The flexible connectors 116 are configured to fold between the corresponding pair of adjacent distal regions 106 when the gastric residence article 100 is in the folded configuration. Following oral administration of the gastric residence article 100, the flexible connectors 116 are configured to unfold when the gastric residence article 100 is in the expanded configuration, thereby applying a force to resist a collapse of the gastric residence article 100 in vivo.

[0047] Each flexible connector 116 is formed in a zigzag pattern created by a plurality of straight segments connected at angular bends to form bends or arcs. The angle at the bends or arcs ranges from 15° to 60°. In an embodiment, when the gastric residence article is in the expanded configuration, the angles may be 15°, 20°, 25°, 30°, 35°, 40°, 45°, 50°, 55°, or 60°. The straight segments meet at a central peak 118 that allows for the folding of the individual flexible connector 116 about the central peak 118. The central peak 118 bends towards a central axis 120 of the gastric residence article 100 when it is in the folded configuration. When the gastric residence article 100 is in the expanded configuration, there is an angle 0° to 90° between the flexible connector 116 and the top plane of the gastric residence article 100.

[0048] The plurality of flexible connectors 116 is made of an alloy. In particular, the flexible connectors 116 is made of at least one material selected from a group consisting of copper-aluminum-nickel alloys, nickel-titanium alloys, iron-based alloys such as Fe-Mn-Si, copper-based alloys such as Cu-Al-Ni.

[0049] Figure 1C illustrates a perspective view of the gastric residence article 100 of Figure 1A in a folded configuration. Figure 1D illustrates a top view of the outer portion 102 of the gastric residence article 100 of Figure 1A in a folded configuration. The foldable central alloy component 108 undergoes elastic deformation when the gastric residence article 100 is in a folded configuration. At this folded configuration, the corresponding distal regions 106, linker components 112, and elongated limb components 114 form triangular prisms that can fit tightly together, allowing for easy storage and oral administration.

[0050] When the gastric residence article 100 is in the folded configuration, all the flexible connectors 116 are folded and contained within gaps formed between the corresponding pairs of adjacent distal regions 106. This allows the flexible connectors 116 to be stored inside the gastric residence article 100. This may advantageously reduce the size of the gastric residence article 100, making it easier to fill it into a capsule while preventing entanglement

during the expansion process of the gastric residence article 100, ensuring smooth expansion in vivo.

[0051] Gaps for storing the folded flexible connectors may be created in these ways:

- (1) The cross-sectional area of the distal regions 106 is smaller than that of the elongated limb component 114. This allows the adjacent elongated limb components 114 to fit together when the gastric residence article 100 is in the folded configuration, while the adjacent distal regions 106 forms the gaps to store the flexible connectors 116.
- (2) The cross-sectional area of the distal regions 106 is small enough to create gaps for storing the flexible connectors 116 when the gastric residence article 100 is folded.
- (3) The sides of the distal regions 106 have grooves. When the gastric residence article 100 is folded, these grooves form the gaps to store the folded flexible connectors 116.

[0052] Figure 1E illustrates a top view of the gastric residence article 100 shown in Figure 1A when it assumes a partially expanded configuration in vivo. Figure 1F illustrates a side view of the gastric residence article 100 of Figure 1E. When the medication is taken, a patient swallows the gastric residence article 100, and the foldable central alloy component 108 recoils in the gastric cavity to allow for the gastric residence article 100 to assume an expanded configuration. When the gastric residence article 100 is in the expanded configuration, the central peak 118 is oriented towards a central axis 120 of the outer portion 102.

[0053] The expanded configuration of the gastric residence article 100 allows it to be retained 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 caused by the peristaltic waves of the stomach compressing the article 100, as shown in Figures 1E and 1F. The plurality of flexible connectors 116 is configured to collectively provide a resistance force in the range of 0 – 2 N to resist a collapse of the gastric residence article 100 in vivo.

[0054] The plurality of flexible connectors 116 is configured to individually increase the force required to bend the gastric residence article 100 from the expanded configuration by 30 degrees, within a range of 0.2-1 N in vivo. In an embodiment, when the gastric residence article 100 is in the expanded configuration, the flexible connectors 116 are in a balanced state without any externally applied force, the resistance force provided by the flexible connectors 116 is 0N. However, when the gastric residence article 100 encounters bending due to peristaltic waves in the stomach, the flexible connectors 116 undergo elastic deformation, generating a resistance force.

[0055] When the gastric residence article 100 resists bending in vivo caused by the stomach's peristaltic waves, the elastic deformation of the flexible connector 116 results in both ends of the flexible connector 116 applying repulsive or tensioning forces on each corresponding pair of adjacent distal regions 106. This action helps resist the collapse of the gastric residence article 100 in vivo.

[0056] After a certain period in the gastric environment, the linker components 112 become structurally compromised. This process makes the linker components 112 flexible or causes them to break apart, allowing for bending or disconnection of the elongated limb components 114 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.

[0057] 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 regions 106 limits the movement of the elongated limb component 114 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 50 D 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 114 in vivo relative to the foldable central alloy component 108. Consequently, the gastric residence article 100 may lose its shape and discharge from the gastric cavity prematurely. The connection of both ends of the flexible connector 116 to a relatively harder distal region 106 also aids in securing both ends of the flexible connector 116.

[0058] 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 alloy component 108. Therefore, when the gastric residence article 100 is in the expanded configuration, the elongated limb components 114 will not bend relative to the foldable central 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.

[0059] 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.

[0060] 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 the gastric environment, and the gastric residence article 100 assumes an expanded configuration as the foldable central alloy component 108 recoils in vivo.

[0061] In an embodiment, the foldable central alloy component 108 includes at least one 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.

[0062] In another embodiment, the foldable central 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.

[0063] Shape memory alloys belong to the family of superelastic alloys. A suitable shape memory alloy for the foldable central alloy component 108 has an austenite transformation finish temperature (A_f) slightly below normal body temperature. At temperatures below the A_f (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 A_f , 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.

[0064] Figure 1G illustrates a transparent view of the outer portion 102 of the gastric residence article 100 depicted in Figure 1A. The plurality of flexible connectors 116 is sequentially connected to form a unitary construction with two ends 122, 124. The two ends 122, 124 of the unitary construction are connected to one distal region 106 to form individual locking mechanisms in the form of hooks for secure attachment. As shown in Figure 1G, the hooks are embedded in the one distal region 106.

[0065] The embodiment disclosed in Figure 1G shows that the plurality of flexible connectors 116 form a unitary construction, and the two ends of the unitary construction are embedded in a distal region 106. In an alternate embodiment, the two ends of the unitary construction may be connected outside the plurality of distal regions to form secure attachment with each other. Furthermore, in an alternate embodiment, the flexible connectors 116 may not form a unitary construction, and each of the flexible connectors 116 may comprise two ends that form individual locking mechanism with the corresponding distal regions 106 for secure attachment.

[0066] The embodiment disclosed in Figures 1A-1G shows that the flexible connectors 116 have a wire structure. It will be appreciated by a person skilled in the art that the flexible connectors 116 can be formed in other structures, such as a tube, a ribbon, and a hollow disc.

[0067] The embodiment disclosed in Figures 1A-1G shows that the flexible connectors 116 are disposed between each corresponding pair of adjacent distal regions 106 to connect them. It will be appreciated by a person skilled in the art that the gastric residence article 100 may not necessarily incorporate flexible connectors 116 between every pair of adjacent distal regions 106. Instead, they may be present only between specific distal regions 106.

[0068] A flexible connector 116 in the wire structure can be formed by encasing it within a mold during the heat treatment process. A flexible connector 116 in the tube structure can be formed by layer cutting a superelastic tube. By selecting a superelastic tube with the appropriate diameter and thickness, the properties of the flexible connectors 116 can be tailored to specific requirements, allowing for versatility in design and functionality. A flexible connector 116 in the tube structure can be formed by stamping processes, followed by shape forming during the heat treatment process. This approach involves initially stamping a flat

sheet or strip of material and then shaping it into a desired shape as part of the heat treatment procedure.

[0069] Figure 2A illustrates a schematic diagram showing a gastric residence article 200A in an expanded configuration in accordance with another example embodiment. Figure 2B illustrates a schematic diagram showing a gastric residence article 200B in an expanded configuration in accordance with a further example embodiment. As shown in Figures 2A and 2B, the outer portion 202A, 202B consists of a central region 204A, 204B and a plurality of distal regions 206A, 206B radially connected to the central region 204A, 204B. In these embodiments, the gastric residence article 200A, 200B further comprises a plurality of flexible connectors 208A, 208B.

[0070] The flexible connectors 208A, 208B form a unitary construction with the outer portion 202A, 202B. More specifically, in the embodiment depicted in Figure 2A, the flexible connectors 208A form a unitary construction with the distal regions 206A of the outer portion 202A. In the embodiment depicted in Figure 2B, the flexible connectors 208B form a unitary construction with the central region 204B of the outer portion 202B.

[0071] Each flexible connector 208 A, 208B includes two curve portions that converge at a central peak. These curves create an arc with a radius exceeding 5 mm, and the central peak is oriented towards the central axis 210A, 210B of the outer portion 202A, 202B when the gastric residence article 200A, 200B is in the folded configuration.

[0072] Each flexible connector 208A, 208B comprises a central peak that bends toward the central axis 210A, 210B of the gastric residence article 200A, 200B, with its two ends folded around this peak. In Figure 2A, the embodiments illustrate that each flexible connector 208A consists of a rod integrated into the outer portion, forming an arc along with the central peak. A skilled person in this field would recognize that the central peak could take on other structures, possibly angular in nature. In an alternative design, the rod extends in the width direction to create a thin plate, mirroring the arc of the original rod, as depicted in Figure 2B.

[0073] When the gastric residence article 200A, 200B is in a folded configuration, the rod or plate are folded and are contained within gaps formed between the corresponding pairs of adjacent distal regions 206A, 206B. As the gastric residence article 200A, 200B expands, an

angle between 0° to 90° is formed between the flexible connector 208A, 208B and the top plane of the gastric residence article 200A, 200B.

[0074] In terms of material properties, the flexible connector 208A, 208B is characterized by its relatively low hardness on the shore hardness scale, measuring between 20 A and 50 D, to facilitate easy folding of the gastric residence article 200A, 200B. However, it possesses a robust Young's Modulus value, exceeding 15 MPa, which can help prevent sideways fractures of the flexible connector 208A, 208B. The flexible connector 208 A, 208B 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.

[0075] The embodiment disclosed in Figures 2A and 2B shows that the flexible connectors 208A, 208B form a unitary construction with the distal regions 206A, 206B. In an alternate embodiment, the flexible connectors 208A, 208B can form a unitary construction with the central region 204A, 204B of the outer portion 202A, 202B.

[0076] Figure 3 illustrates a schematic diagram showing a gastric residence article 300 in an expanded configuration in accordance with another example embodiment. The gastric residence article 300 includes an outer portion 302, including a flexible connector in the form of a membrane 304. In this embodiment, the membranes 304 form a unitary construction with the outer portion 302. Specifically, the outer portion 302 has a central region 306 and a plurality of distal regions 308 radially connected to the central region 306. The central region 306 comprises multiple arms 310 for connecting to the corresponding distal regions 308. The membranes 304 form a unitary construction with the central region 306 of the outer portion 302, and they are positioned between each corresponding pair of adjacent arms 310, effectively serving as connectors between the adjacent arms 310.

[0077] The gastric residence article 300 further includes a plurality of linker components 312. Each linker component 312 has a first side and a second side opposite the first side. The first sides of the linker components 312 are individually connected to their corresponding distal regions 306. The plurality of linker components 312 is configured to be structurally compromised in vivo, resulting in a loss of a shape of the gastric residence article 300. The gastric residence article 300 further includes a plurality of elongated limb components 314. Each elongated limb component 314 is individually connected to the second side of a corresponding linker component 312. At least one of the elongated limb components 314 has

an active substance, such as a therapeutic agent or a diagnostic agent, for delivering gastroretentive drug at a predetermined rate.

[0078] In terms of structural and material properties, the membranes 304 have a thickness of 0.3 - 0.8 mm. The membrane 304 is characterized by its relatively low hardness on the shore hardness scale, measuring not more than 50 D, to facilitate easy folding of the gastric residence article. However, it possesses a robust Young's Modulus value, exceeding 15 MPa, which can help prevent sideways fractures of the membrane 304. The membrane 304 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.

[0079] The embodiment disclosed in Figure 3 shows that the membranes 304 form a unitary construction with the central regions 306. In an alternate embodiment, the membrane 304 can form a unitary construction with the distal regions 308 of the outer portion 302.

[0080] Gastric retention plays a pivotal role in ensuring the proper functioning of the gastric residence article. This is especially crucial given the natural gastric emptying process, which exerts a force that could potentially compress the gastric residence article, making it small enough to exit through the pyloric opening. However, the flexural strength of the foldable central alloy component alone may not be sufficient to withstand the external forces imposed by the external force caused by peristaltic movements. Thus, additional mechanisms may be required to reinforce gastric retention, ensuring that the gastric residence article remains within the stomach for the necessary duration.

[0081] Embodiments of the present invention provide a plurality of flexible connectors that is positioned between the distal regions. When the gastric residence article is in its expanded configuration, the flexible connectors extend laterally, creating tension between the distal regions, which in turn resists any folding of the article. This biasing force effectively works to keep the gastric residence article in an expanded and taut state, thereby preventing it from leaving the gastro chamber prematurely. This is of utmost importance, as without this counterforce, the gastric residence article might not be able to maintain its shape, potentially causing it to exit the chamber prematurely.

EXAMPLE 1

An example of the gastric residence article described in Figure 1A is provided below.

[0082] 0.35 mm thick Nitinol plates are stamped to obtain the foldable central alloy component. The central region and distal regions of the outer portion are formed by injecting PC-3575A and PC-3572D from Lubrizol respectively.

[0083] 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 3 mm segments to form the linker components.

[0084] 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.

[0085] The outer portion, foldable central alloy component, linker components, and elongated limb components are then loaded into a customized mold and heat fused together using a laser to form the gastric residence article.

[0086] In this example, the individual flexible connector is formed in a wire structure made of nickel-titanium alloys.

[0087] The capsules containing the gastric articles were then fed to Labradors. X-ray of the abdomen were conducted every day to determine the retention periods in the abdomen. It was found that the gastric retention device can be retained in the Labradors's stomach for more than 10 days.

EXAMPLE 2

[0088] An example of the gastric residence article described in Figure 1G is provided below.

[0089] The plurality of flexible connectors is sequentially connected to form a unitary construction with two ends that form individual locking mechanisms at one distal region for secure attachment. The locking mechanisms comprises the two ends forming individual hooks embedded in the one distal region.

[0090] The capsules containing the gastric articles were then fed to Labradors. X-ray of the abdomen were conducted every day to determine the retention periods in the abdomen. It was found that the gastric retention device can be retained in the Labradors's stomach for more than 10 days.

EXAMPLES 3-7

[0091] An example of the gastric residence article described in Figure 2A is provided below.

[0092] Each flexible connector comprises an elastic rod that forms a unitary construction with the outer portion. the rod of the gastric retention article in Examples 3-7 are respectively made of CL 2000X(3A)、GP2810-20N(20A)、PC3575A 、Covestro 1350D、TT-2075D-B40. The elastic rod form an arc, wherein the arc bends towards the central axis of the gastric residence article when the gastric residence article is in the expanded configuration.

[0093] The gastric retention article of Examples 4-6 can be retained in the Labradors's stomach for more than 8 days.

[0094] The gastric retention article of Examples 3 can be retained in the Labradors's stomach for less than 3 days.

[0095] The gastric retention article of Examples 7 cannot be folded successfully.

EXAMPLES 8-10

[0096] An example of the gastric residence article described in Figure 3 is provided below.

[0097] The flexible connector comprises a membrane that forms a unitary construction with the outer portion. The membrane of the gastric retention article in Examples 8-10 are respectively made of PC3575A, Covestro 1350D, TT-2075D-B40 and has a thickness of 0.5

mm. The membrane occupies 60% of the plane space between each corresponding pair of adjacent arms of the outer portion.

[0098] The gastric retention article of Examples 8-9 can be retained in the Labrador's stomach for more than 8 days.

[0099] The gastric retention article of Examples 10 cannot be folded successfully.

[0100] 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:
 - an outer portion comprising a central region and a plurality of distal regions radially connected to the central region;
 - a foldable central alloy component securely received within the outer portion, wherein the foldable central alloy component is configured to undergo elastic deformation when the gastric residence article is in a folded configuration and to recoil to allow for the gastric residence article to assume an expanded configuration;
 - a plurality of linker components, 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 distal region; and
 - a plurality of elongated limb components comprising an active substance, each elongated limb component being individually connected to the second side of a corresponding linker component, and the active substance being a therapeutic agent or a diagnostic agent,
 - a plurality of flexible connectors connecting corresponding pairs of adjacent distal regions, wherein the flexible connectors are configured to fold when the gastric residence article is in the folded configuration and to unfold when the gastric residence article is in the expanded configuration, thereby applying force to resist a collapse of the gastric residence article in vivo,
 - wherein the plurality of linker components is configured to be structurally compromised in vivo, thereby resulting in a loss of a shape of the gastric residence article.
2. The gastric residence article as claimed in claim 1, wherein when the gastric residence article is in the folded configuration, the plurality of flexible connectors is folded such that all the flexible connectors are contained within gaps formed between the corresponding pairs of adjacent distal regions.
3. The gastric residence article as claimed in claim 1 or 2, wherein each flexible connector includes a central peak that bends towards a central axis of the gastric residence article when the gastric residence article is in the folded configuration.
4. The gastric residence article as claimed in any one of the preceding claims, wherein the plurality of distal regions has a higher level of hardness than the central region.

5. The gastric residence article as claimed in any one the preceding claims, wherein the plurality of flexible connectors is secured to the corresponding pair of adjacent distal regions.
6. The gastric residence article as claimed in any one of the preceding claims, wherein the individual flexible connector is formed in a structure selected from a group consisting of a wire, a tube, a ribbon, and a hollow disc.
7. The gastric residence article as claimed in claim 1, wherein the plurality of flexible connectors is sequentially connected to form a unitary construction with two ends.
8. The gastric residence article as claimed in claim 7, wherein the two ends of the unitary construction are connected to one distal region to form individual locking mechanisms for secure attachment.
9. The gastric residence article as claimed in claim 8, wherein the locking mechanisms comprise the two ends forming individual hooks embedded in the one distal region.
10. The gastric residence article as claimed in claim 7, wherein the two ends of the unitary construction form secure attachment with each other outside the plurality of distal regions.
11. The gastric residence article as claimed in claim 1, wherein each of the flexible connectors comprises two ends that form individual locking mechanism with the corresponding distal regions for secure attachment.
12. The gastric residence article as claimed in any one of the preceding claims, wherein the plurality of flexible connectors is made of an alloy.
13. The gastric residence article as claimed in claim 12, wherein the flexible connector is made of at least one material selected from a group consisting of copper-aluminum-nickel alloys, nickel-titanium alloys, iron-based alloys, copper-based alloys.
14. The gastric residence article as claimed in claim 1, wherein the plurality of flexible connectors forms a unitary construction with the outer portion.
15. The gastric residence article as claimed in claim 14, wherein each flexible connector comprises an arc that forms a unitary construction with the outer portion.

16. The gastric residence article as claimed in claim 15, wherein the arc has a hardness level of between 20 A and 50 D on the shore hardness scale.
17. The gastric residence article as claimed in claim 15 or 16, wherein the arc has a Young's Modulus value of more than 15 MPa.
18. The gastric residence article as claimed in any one of claims 15 to 17, wherein the arc 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.
19. The gastric residence article as claimed in claim 14, wherein each flexible connector comprises a membrane that forms a unitary construction with the outer portion.
20. The gastric residence article as claimed in claim 19, wherein the membrane has a thickness of 0.3 - 0.8 mm.
21. The gastric residence article as claimed in claim 19 or 20, wherein the membrane has a hardness level of not more than 50 D on the shore hardness scale.
22. The gastric residence article as claimed in any one of claims 19 to 21, wherein the membrane has a Young's Modulus value of more than 15 MPa.
23. The gastric residence article as claimed in any one of claims 19 to 22, wherein the membrane 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.