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Research progress of biodegradable staples in gastrointestinal anastomosis

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Highlights

- Biodegradable staples have high biodegradability, good mechanical, and biocompatibility properties.
- The mechanical properties of biodegradable staples can be adjusted by structure optimizations.
- Biodegradable staples will be widely used in gastrointestinal anastomosis.

Abstract

Since the 1960s, anastomosis instruments have become integral in gastrointestinal procedures. These staples, however, remain permanently in the body, potentially inciting inflammatory reactions, compromising imaging effects of computed tomography scans, and causing diagnostic inaccuracies. This scenario underscores the imperative for biodegradable surgical staples, spurring research into materials that exhibit both superior biodegradability and mechanical integrity. Current investigations are focused on Magnesium (Mg), Zinc (Zn), and their alloys for their exemplary biodegradability, mechanical strength, and biocompatibility, making them promising candidates for gastrointestinal anastomosis. This review encapsulates the latest advancements in biodegradable surgical staples, emphasizing material and structural enhancements. It details the mechanical attributes of wires intended for staple fabrication, the corrosion dynamics across varied environments such as in vitro immersion solutions and in vivo implantation sites and the impact of structural refinements on staple biodegradability. Additionally, it contrasts the benefits and limitations of Mg-based and Zn-based staples and offers insights into the potential and hurdles in developing biodegradable surgical staples, thereby fostering further exploration in this field.

Keywords: Surgical staple, gastrointestinal anastomosis, biodegradable material, structural optimization, finite element analysis

Introduction

In clinical settings, surgical staples, predominantly crafted from Titanium (Ti) alloy, have revolutionized the healing and reconstruction processes in gastrointestinal anastomosis, spanning the gastrointestinal tract to the small intestine [1-3]. Staples offer advantages over traditional suturing by reducing operative durations, minimizing postoperative complications, and alleviating patient discomfort [4]. Nevertheless, the permanent presence of Ti alloy staples within the body can provoke inflammatory responses and other severe complications [5]. Thus, there is a pressing need for the development of biodegradable staples, which promise to eliminate long-term adverse effects associated with their non-degradable counterparts [6]. Since 2016, biodegradable staples have garnered significant attention for their potential in facilitating the healing and reconstruction of the stomach and intestinal tract [7].

In traditional gastrointestinal anastomosis, the paramount considerations for surgical staples are adequate mechanical strength, optimal blood supply, and the absence of tension, all of which are crucial for effective wound healing [8]. The diverse implantation environments within gastrointestinal anastomosis, including varying

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Table 1. Recent studies on biodegradable surgical staples in gastrointestinal anastomosis

Materials	The yield tensile strength	The ultimate tensile strength	Elongation	Soak solution	Corrosion behavior	Experimental animal type	The implantation cycle	Reference
HP Mg (Ø 0.26 mm, 2016)	147 ± 8 MPa	196 ± 5 MPa	14.6 ± 5%	The m-SBF	The staples were not absorbable completely for 9 weeks and the remained part kept homogeneous shape without fracture.	Pigs (stomach)	9 weeks	[7]
HP Mg (Ø 0.26 mm, 2017)	147 ± 8 MPa	196 ± 5 MPa	14.6 ± 5%	The intestinal juice/Hanks' solution	0.49 mm/year (intestinal juice) / 0.34mm/year (Hanks' solution)	Adult minipigs (small intestine)	1 month	[10]
HP Mg (Ø 0.26 mm, 2017)	147 ± 8 MPa	196 ± 5 MPa	14.6 ± 5%			Mice (rectal)	7 days	[11]
HP Mg (Ø 0.26 mm, 2021)	147 ± 8 MPa	196 ± 5 MPa	14.6 ± 5%	The m-SBF	The degradation rate of 3.1 mm/year on the 3rd day and then the corrosion rate gradually tended to be about 1 mm/year.	New Zealand rabbits (small intestine)	7 weeks	[12]
Mg-6Zn (Ø 1 mm, 2013)	169.5 ± 3.6 MPa	279.5 ± 2.3 MPa	18.8 ± 0.8%	The intestinal juice	0.16 mm/year(in vitro) / 2.32 mm/year(in vivo)	Sprague–Dawley rats (cecum)	4 weeks	[13]
Mg-5Zn (Ø 0.23mm, 2023)				The HBSS/ SCF	The staples in SCF degraded at a faster rate in the first 3 days, approximately three times higher than those in Hanks' solution.			[14]
ZN20 (Ø 0.23mm, 2021)		256 ± 8 MPa	12.56% ± 0.66%	Drainage fluid from the abdomen andsplenic fossa, the gastric tube, and the duodenum	The staples in vitro corroded completely within 6 days / The staples in vivo corroded completely within about 8 weeks.	Female New Zealand rabbits (stomach and intestine)	1, 2, 4 and 8weeks	[16]
FA sorb Mg™ (Ø 0.25mm, 2019)	260 ± 0 MPa	290 ±1 MPa	22 ± 1%	The artificial intestinal juice	The products of corrosion covered all staples after four days of immersion	Female adult pigs (small intestine)	4 weeks	[18]
AZ31 (Ø 0.3mm, 2023)		302 ± 4MPa	23 ± 3%	The SCF	The staples remained in its integrated structure after 7 days and completed degradation after 90 days.	Beagle dogs (colon)	7 days (6 dogs) and 90 days (18 dogs)	[4]
Zn alloy 1) / Zn alloy 2) / Zn alloy 3 (Ø 0.4mm, 2020)		212/198/ 200 MPa	19/7/21%	The FeSSIF and HBSS	The corrosion rates of Zn alloy staples 1, 2, and 3 were 0.02 mm/year in HBSS and 0.12, 0.11, and 0.13 mm/year in FeSSIF.	Male New Zealand white rabbits (stomach)	1, 4, 12 weeks	[19]
Zn-0.8 wt.% Li-0.1 wt.% Mn (Ø 0.3 mm, 2020)	390.12 ± 12.45 MPa	530.16 ± 1.62 MPa	68.89 ± 2.68%	The Hanks' solution and SGF	0.843 ± 0.003 mm/year (SGF) / 0.191 ± 0.009 mm/year (Hanks' solution)	Mini fragrant pigs (stomach and intestine)	3 days, 8 weeks, and 12 weeks	[5]

Note: HP Mg, high-purity Magnesium; m-SBF, modified simulated body fluid; Zn, Zinc; Ti, Titanium; HBSS, hank's balanced salt solution; SCF, simulated colon fluid; ZN20, Mg-2Zn-0.5Nd; FA sorb Mg™, Mg-2.5Nd-1Y; Zn alloy 1, Zn-1.0Cu-0.2Mn-0.1Ti; Zn alloy 2, Zn-1.0Mn-0.1Ti; Zn alloy 3, Zn-1.0Cu-0.1Ti; FeSSIF, fed-state simulated intestinal fluid; SGF, simulated gastric fluid.

Table 2. Main characteristics of staples used in gastrointestinal anastomosis

Materials	Advantages	Disadvantages
Ti-based alloys	High biocompatibility and corrosion resistance, fatigue strength, light weight.	Lack of biodegradability.
HP Mg / Mg-based alloys	Biodegradable, excellent biocompatible, broad range of mechanical strength, pro-wound healing degradation products.	Fast corrosion rate, hydrogen gas evolution during biodegradation, prone to stress corrosion cracking.
Zn-based alloys	Biodegradable, good biocompatible, moderate corrosion resistance	Prone to age hardening and creep.

Note: This table was cited from [9, 21]. Ti, Titanium; HP Mg, high-purity Magnesium; Zn, Zinc.

tissues such as the stomach, small intestine, and rectum, present significant challenges in the development of biodegradable staples for these procedures [9]. Unlike conventional staples, biodegradable surgical staples not only must provide robust support throughout the entire healing process without failure but also must degrade safely at a controlled rate within the complex environment of human body, gradually relinquishing their load-bearing capacity as tissues recover [3]. Hence, the research in terms of biodegradable surgical staples include corrosion and the biocompatibility of Magnesium (Mg) / Zinc (Zn)-based alloy staples in vitro and in vivo, and their mechanical properties.

This review delineates advancements in biodegradable surgical staple technology, focusing on mechanical attributes, corrosion rates across different in vitro and in vivo environments, and the impact of structural enhancements on the performance of these staples, as detailed in **Table 1**. Specifically, it explores the leading Mg-based and Zn-based materials for gastrointestinal anastomosis applications, discussing the deployment strategies of these materials in various implantation sites through both in vitro and in vivo studies. Ultimately, it underscores the challenges associated with employing Mg/ Zn-based surgical staples in clinical settings.

Biodegradable surgical staples composed of Mg and its alloys

High-purity (HP) Mg anastomotic staples

In the evolution of biodegradable surgical staples, HP Mg staples have been subject to extensive examination. The inaugural HP Mg staples, designed for gastric anastomosis, were introduced in 2016 [7]. To circumvent stress corrosion after being closed, these staples were engineered with an interior angle of 100°, altering the distribution of residual stress. After nine-week post-implantation in pigs, the HP Mg staples showed robust support and excellent biocompatibility for stomach anastomosis. Subsequently, Qu et al. documented the application of HP Mg staples in small intestine anastomosis of minipigs, demonstrating their ability to provide ample support over one month [10]. Furthermore, the integration of Mg staples into tissue didn't generate complications, and the in vivo degradation rate of these bridging surgical staples was determined to be 0.007 mm per month.

More in-depth research was carried since the discover of that HP Mg staples could influence wound healing processes. In 2017, Xia et al. reported that HP Mg staples could mitigate inflammatory responses in rectal anastomoses by modulating the activities of signaling growth factors [11]. More recently, in 2021, Zan et al. employed HP Mg staples in intestinal closure studies, uncovering their antitumor effects [12]. The release of Mg ions and hydrogen from HP Mg staples, both in vitro and in vivo, was found to inhibit the recurrence of residual tumor cells. These research attests to the excellent biodegradability of HP Mg anastomotic staples, and their wound healing potential, paving the way for further detailed investigations.

Although HP Mg staples have demonstrated adequate support, favorable biocompatibility, and effective wound healing capabilities in various studies, skepticism remains regarding their clinical application. Concerns particularly revolve around the corrosion rate, hydrogen gas evolution, and stress corrosion during the degradation process, as outlined in **Table 2**. This table was cited from [9, 21]. Consequently, the future research will delve into the safety of HP Mg staples for human use in gastrointestinal anastomosis.

Biodegradable surgical staple composed of Mg alloys

The exploration of gastrointestinal anastomosis utilizing Mg-Zn alloys initially diverged into various methodologies. In 2013, Yan et al.

pioneered the study of Mg-6Zn stapler pins by evaluating their impact on rat cecum incisions, marking the first investigation into the application of Mg-Zn alloys for stapler pins in intestinal reconstruction [13]. Following this, Cheng et al. examined the degradation behavior and practicality of Mg-5Zn staples, finding that these staples degraded uniformly in simulated colon fluid and maintained their effectiveness up to ten days [14]. In 2021, Song et al. explored the potential of Mg-2Zn-0.5Nd (Zn20) alloy as a material for surgical nails [15]. They employed Zn20 alloy wires and surgical sutures to secure the lower margin of the stomach in New Zealand rabbits. In the same year, Gao et al. documented the successful deformation of staples made from Zn20 alloy from a U-shape to a B-shape, demonstrating that Zn20 staples possessed adequate mechanical support for anastomosis with a bursting pressure of 40 kPa [16]. In a subsequent study in 2022, Zhang et al. reported that Mg-6Zn-1Mn staples not only showcased high strength (340 MPa) but also displayed satisfactory ductility (10%) [17]. Significantly, the mechanical integrity of the staples was enhanced to 90 hours post-processing by incorporating protein, with all rabbits making a full recovery and resuming normal oral intake.

Beyond the Mg-Zn alloy staples, several other Mg-based staples with superior mechanical properties have been explored for gastrointestinal anastomosis applications. In 2019, Amano et al. highlighted the enhanced mechanical properties of Mg-2.5Nd-1Y (FA sorb Mg™) staples, which demonstrated a yield tensile strength of 260 MPa, an ultimate tensile strength of 290 MPa, and an elongation at break of 22% [18]. The study revealed that FA sorb Mg™ staples could provide robust support for the healing of small intestines. In a 2022 study, Zhang et al. introduced an AZ31 staple designed for colonic anastomosis [4]. Notably, they achieved a moderate degradation rate aligned with the tissue healing timeline for colonic anastomosis through micro-arc oxidation treatment and further enhanced by coating the AZ31 alloy staples with poly-L-lactic acid. The colon wounds exhibited complete recovery after 90 days post-operation, with no instances of leakage or stenosis. Additionally, all 12 dogs in the study fully recovered without any trace of element accumulation in their organs, and no severe inflammation, tissue necrosis, or abnormal hyperplasia was observed during implantation.

While these Mg alloy staples provide adequate support, exhibit desirable biodegradation, and maintain good biocompatibility, the incorporation of other elements into surgical staples for use in human gastrointestinal anastomosis necessitates further investigation. Consequently, a prolonged period of study is essential for Mg alloy staples intended for gastrointestinal anastomosis applications.

Biodegradable surgical staples composed of Zn Alloy

Research on Zn-based alloys for surgical staples is a relatively recent development, with the inaugural study by Amano et al. in 2020 marking a significant milestone. This study explored three Zn alloys (Zn-1.0Cu-0.2Mn-0.1Ti, Zn-1.0Mn-0.1Ti, and Zn-1.0Cu-0.1Ti) as potential materials for gastric resection staples [19]. The Zn alloy staples demonstrated adequate support for gastro-restriction applications during in vivo implantation. Moreover, this study noted tissue inflammatory responses post-implantation, indicating the short-term safety of these Zn-based staples in animal models. Subsequently, Guo et al. introduced a gastrointestinal staple composed of a Zn-0.8Li-0.1Mn alloy, showcasing impressive mechanical properties, including yield tensile strength, ultimate tensile strength, and elongation at 390 MPa, 530 MPa, and 69%, respectively [5]. These Zn-Li-Mn staples exhibited a slower corrosion rate (0.191 ± 0.009 mm/year) in Hanks' solution compared to HP Mg staples (0.34 mm/year), with 89% of the staple remaining after 12 weeks of implantation. The advantages of Zn-based staples lie in their degradation mechanisms: no gas generation, formation of a compact degradation product, good biocompatibility, moderate corrosion resistance, and superior mechanical properties.

Although Mg screws and stents have been utilized clinically, Mg-based staples have yet to advance to clinical trials, with knowledge confined to in vivo studies [8, 20]. The rapid corrosion rate, hydrogen gas evolution, and susceptibility to stress corrosion cracking limit the application of Mg-based staples. In contrast, the slower corrosion rate of Zn alloys allows for a more extended retention of mechanical integrity in staples, despite their susceptibility to age hardening and creep [21]. Nonetheless, current research on Zn-based staples in gastrointestinal anastomosis has their limitations, indicating a need for more detailed studies.

Structural optimizations of biodegradable surgical staples

To enhance the efficacy of biodegradable surgical staples in clinic, structural optimization

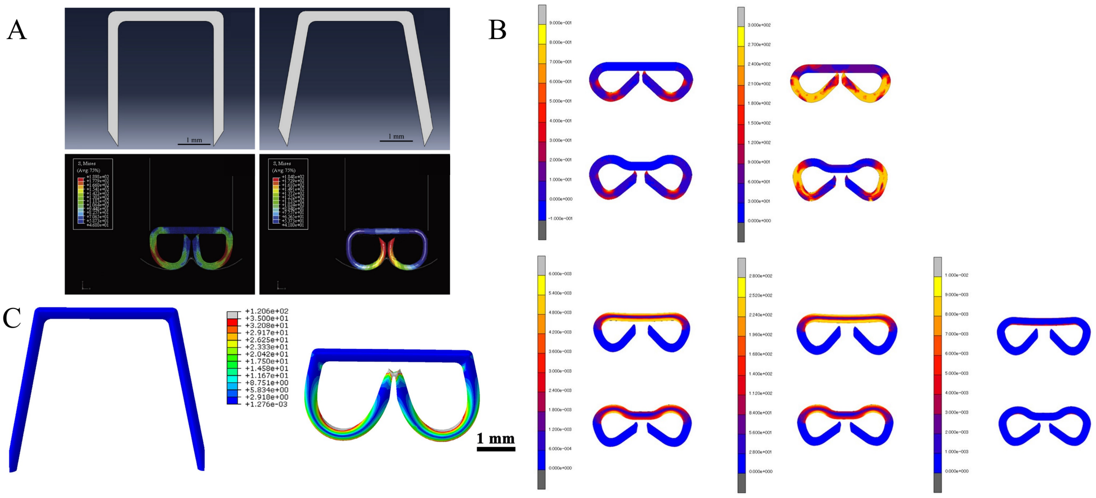

Figure 1. Structural optimizations of biodegradable surgical staples. (A) Structural design and finite analysis on the high-purity Magnesium staple; (B) The Mg-2.5Nd-1Y staple; (C) The Zn-0.8Li-0.1Mn staple. This figure was cited from [5, 7, 18]. Mg, Magnesium; Zn, Zinc.

has emerged as a pivotal strategy for improving the integrity of biodegradable anastomoses. In 2016, Wu et al. undertook a study to refine the design of HP Mg staples for gastric anastomosis through Finite Element Analysis [7]. They designed the shape of staples in a U-form with interior angles of 90° and 100°, as depicted in **Figure 1A** [7]. The Finite Element Analysis identified the staple with a 100° interior angle as optimal, effectively distributing residual stress at the staple's tip upon closure to mitigate stress corrosion risk. Gao et al. further elucidated that tensile stress applied to an HP Mg bar could hasten its in vitro corrosion, resulting in significant pitting and stress corrosion cracking [22]. This finding underscores the influence of tensile stress on the corrosion behavior of HP Mg. Aiming to alleviate stress and strain concentration at the junction of staple legs, Amano et al. innovated the crown design of FA sorb Mg™ staples, which has a more rounded shape that eliminates sharp bends, as illustrated in **Figure 1B** [18]. Subsequently, the study by Guo et al. revealed that the redesign of Zn-0.8Li-0.1Mn staples to incorporate chamfers, shown in **Figure 1C**, led to a primary concentration of residual stress on the legs and arc of the staple [5]. This structural optimization not only alters staple deformation but also impacts stress/strain distribution. Given the sensitivity of biodegradable materials to stress and strain, structural optimization presents a crucial method for reinforcing anastomosis with biodegradable staples.

Conclusion

Biodegradable surgical staples are designed to temporarily secure wounded tissue during the healing process, providing clear benefits over traditional permanent staples by minimizing post-surgical complications. The effectiveness of these staples, especially in gastrointestinal anastomosis, hinges on their ability to meet varied mechanical and biodegradation requirements, influenced by the healing rates and tissue types involved. Through careful selection of materials and structural refinement via finite element analysis, the practicality of biodegradable staples has been enhanced. Nonetheless, current researches on Mg/Zn-based alloys tend to overlook critical factors such as corrosion rate, age-hardening, creep, and corrosion fatigue. Addressing these aspects is crucial for a comprehensive evaluation of material suitability for gastrointestinal anastomosis applications, ensuring that biodegradable staples can reliably perform throughout the wound remodeling period.

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