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Review

Innovative Gastrointestinal Drug Delivery Systems: Nanoparticles, Hydrogels, and Microgrippers

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Abstract

Over the past decade, new technologies have emerged to increase intrinsic potency, enhance bioavailability, and improve targeted delivery of drugs. Most pharmaceutical formulations require multiple dosing due to their fast release and short elimination kinetics, increasing the risk of adverse events and patient non-compliance. Due to these limitations, enormous efforts have focused on developing drug delivery systems (DDSs) for sustained release and targeted delivery. Sustained release strategies began with pioneering research using silicone rubber embedding for small molecules and non-inflammatory polymer encapsulation for proteins or DNA. Subsequently, numerous DDSs have been developed as controlled-release formulations to deliver systemic or local therapeutics, such as small molecules, biologics, or live cells. In this review, we discuss the latest developments of DDSs, specifically nanoparticles, hydrogels, and microgrippers for the delivery of systemic or localized drugs to the gastrointestinal (GI) tract. We examine innovative DDS design and delivery strategies tailored to the GI tract's unique characteristics, such as its extensive length and anatomical complexity, varying pH levels and enzymatic activity across different sections, and intrinsic peristalsis. We particularly emphasize those designed for the treatment of inflammatory bowel disease (IBD) with *in vivo* preclinical studies.

Keywords: sustained release; targeted delivery; gastrointestinal tract; inflammatory bowel disease; pharmacokinetics

1. Introduction

Gastrointestinal drug delivery—including oral and rectal delivery—is still considered the preferred method of administering drugs as it is more user-friendly, non-invasive, and generally more cost-effective compared to injectables or intravenously delivered drugs. In addition, the length and complexity of the gastrointestinal (GI) tract make it an ideal target for technologies that aim at improving drug delivery, increasing drug potency, and enhancing bioavailability [1]. Furthermore, the GI tract displays great ability for drug absorption, owing to its large intestinal surface area and rich mucosal vasculature [2] which can also be advantageous when targeting drugs to diseases of the GI tract mucosa, such as in the treatment of inflammatory bowel disease (IBD) [3]. However, despite being a favorable route of drug delivery, the GI tract has several constraints, including the low pH in the stomach, the presence of digestive enzymes in the intestine, rapid transit times, and barriers such as mucus lining the epithelium. These factors significantly affect drug stability, retention time, absorption, and overall bioavailability [1,2].

In this review, we focus on recent developments of drug delivery systems (DDSs) fabricated or formulated at the micro- and nano-scale for effective delivery of active pharmaceutical ingredients (APIs) to the GI tract, specifically, nanoparticles, hydrogels, and microgrippers (Fig. 1 Ref. [4]). For each of these categories, we first present an overview of design principles and formulation techniques, then discuss novel DDSs with particular focus on those studied in animal models for the treatment of IBD.

2. Nanoparticle-Based Systems for Systemic Drug Delivery in the GI Tract and Localized Targeted therapies for IBD

2.1 Overview of Nanoparticle Properties and Design Principles

Nanoparticles (NPs) are materials with sizes ranging from 1 to 100 nm and are characterized with uniform size distribution, favorable surface potential, and low polydispersity index [5,6]. A variety of techniques are used to formulate nanoparticles, such as emulsification [7], nanomilling [8], and nanoprecipitation [9]. NP-based formulations have the potential to improve the stability and solubility of APIs, facilitate their transport across membranes, and prolong circulation times, thereby reducing toxicity, and enhancing bioavailability and efficacy [6,10].

There are three main classes of nanoparticles as drug delivery systems: lipid-, polymer-, or inorganic-NPs [6]. Lipid-NPs are spherical vehicles comprised of a lipid bilayer(s) surrounding one or more internal aqueous compartments. Lipid-NP delivery systems (e.g., liposomes) have several advantages, such as self-assembly, biocom-

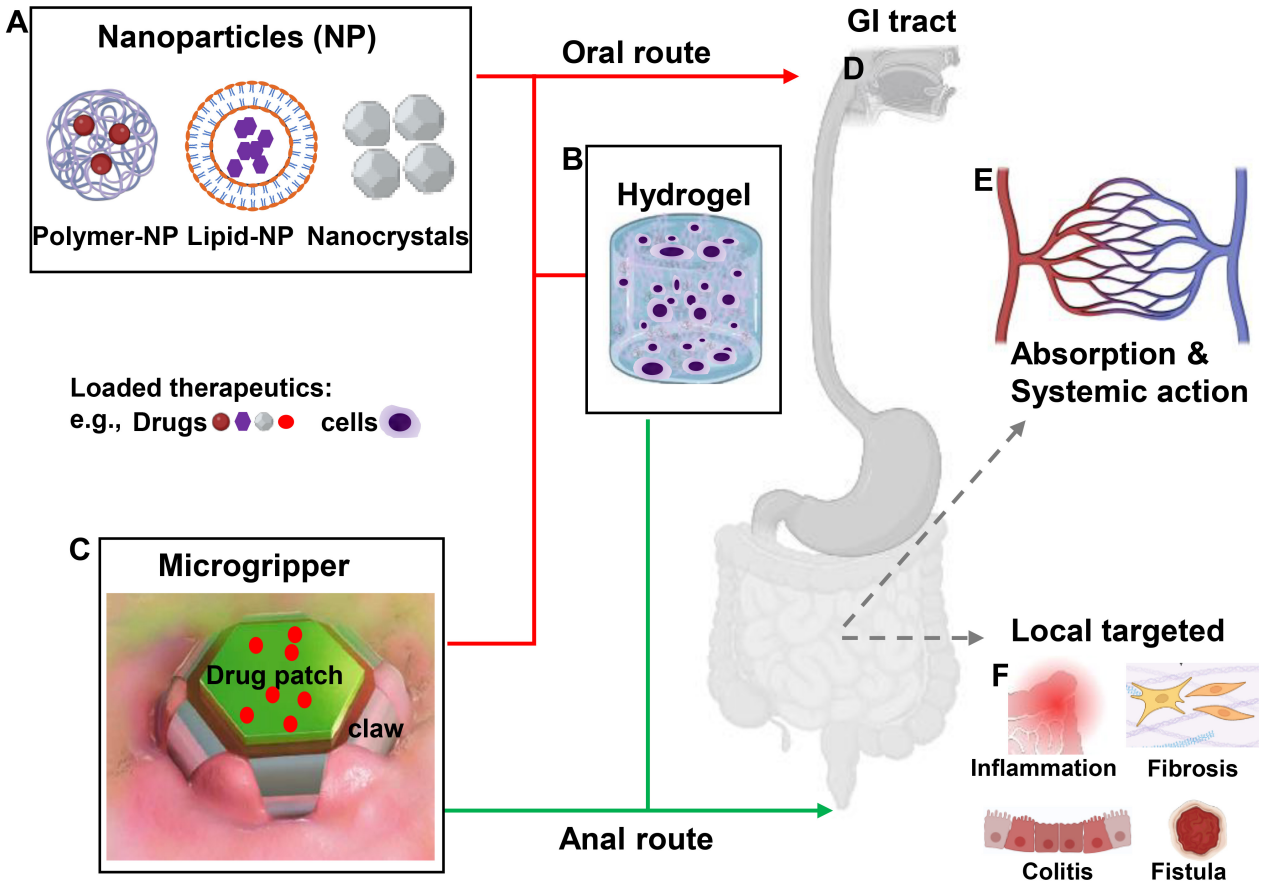

Fig. 1. Overview of drug delivery systems for gastrointestinal (GI) tract delivery. Schematic illustration of main types of nanoparticles (A), hydrogel (B), microgripper (C) (shown is a theragripper latched to mucosal tissue, reproduced with permission from Ghosh *et. al.*, Science Advances; published by the American Association for the Advancement of Science, 2020 [4]), delivery routes through the GI tract (D), and drugs delivered for systemic action (E) or GI-specific local treatment (such as inflammation, fibrosis, colitis, and fistula) (F).

patibility, high bioavailability, and payload flexibility [11]. Polymer-NPs are engineered using biocompatible natural or synthetic polymers, such as hyaluronic acid or poly(lactic-co-glycolic acid). Inorganic-NPs are made from materials that have good biocompatibility and stability [6,12] such as gold, iron oxide, zinc oxide, silver, carbon, silica, boron, hydroxyapatite, and semiconductors [12,13].

The design of NP-based DDSs relies on understanding the mechanisms of biological barriers to therapeutics. Previous reviews have outlined design frameworks to overcome these biological barriers [6,10,14,15]. One of those designs includes incorporating cationic polymers (e.g., poly-ethyleneimine) that effectively increases the release of APIs from NPs confined in endosomal compartments [10]. Another technique entails PEGylation, which results in evasion of mononuclear phagocytes [16–18]. A third technique includes non-spherical NPs resulting in tumbling and rolling dynamics, thereby increasing the probability of blood vessel wall contact and epithelial infiltration [19]. More specifically, several engineering designs have been utilized to surmount obstacles within the GI tract. One approach involves enteric coating with acid-stable Eudragit S100 to prevent premature release in the stomach, enabling targeted delivery in the colon where the polymers dissolve in response to a neutral pH environment [20]. Other examples include encapsulation of APIs with mucoadhesive NPs for prolonged retention time, PEGylation of NPs for proteolytic enzyme resistance, or engineering mucus penetrating systems for enhanced delivery [15]. Table 1 summarizes NP characteristics, advantages, disadvantages, and applications.

2.2 Novel NP Formulations for Oral Delivery of Systemically Acting Drugs

Previously, Cote *et al.* [21] comprehensively reviewed nanomedicines for noncancerous diseases, and summarized 87 NP formulations for targeted delivery in different sites of the GI tract. In this section, we provide an overview of novel NP formulations designed for GI tract delivery of systemic drugs, emphasizing formulations tested in animal models with pharmacokinetics data (**Supplementary Table 1**).

Table 1. Major types of nanoparticles for drug delivery: advantages, disadvantages, and applications.

Characteristics	Advantages	Disadvantages	Applications
Small sizes, ranging from 1 to 100 nm	Enhanced interaction with cellular and subcellular structures	Non-specific distribution causing side effects	Efficient drug delivery and imaging
Unique physical, chemical, and biological properties	Controlled drug release, improved solubility and stability	Immunogenicity	Targeting inflammation, fibrosis, colitis, and wound healing (e.g., fistula)
Uniform size distribution, favorable surface potential, and low polydispersity index	Prolonged circulation time, improved membrane permeability	Toxicity and biocompatibility issues	Guided delivery to disease sites
High surface area to volume ratio	Higher drug loading capacity and controlled release	Challenges in scale up production	Improved anti-inflammation and anti-tumor efficacy via the EPR effect
Tunable surface properties (e.g., polyethylene glycol (PEG) coating)	Targeted drug delivery, enhanced bioavailability, reduced immunity	Translational gap between preclinical studies and approved human use	Evasion of mononuclear phagocytes
Unique optical and magnetic behavior	Imaging and magnetic guided delivery	The novelty and complexity pose challenges for regulatory approval	Increased API release by escaping endosomal compartments
Enhanced cellular uptake	Enhanced Permeability and Retention (EPR) effect		Simultaneous treatment and diagnosis
Composition varieties (e.g., polymers, lipid, inorganic)	Broadened drug categories for GI delivery		
Multifunctionality (e.g., theranostics)	Simultaneous treatment and diagnosis		

Formulations of diabetic drugs: The following three studies reported novel NP formulations for diabetes. One group of researchers employed a self-nanoemulsifying drug delivery system to co-administer sitagliptin and dapagliflozin, demonstrating effective hyperglycemia control in streptozotocin-induced diabetic mice [22]. Two other groups engineered oral form of NPs for delivery of liraglutide or glargine insulin, showing a 2.3-fold higher maximum serum concentration (C_{max}) in oral liraglutide compared with subcutaneous injection in rats [23], and increased efficacy in oral glargine in controlling hyperglycemia in streptozotocin-induced diabetic rats compared to the injected form [24].

Formulations of anti-inflammatory drugs: NP formulations for several anti-inflammatory drugs have shown promising outcomes through oral administration. A chitosan-based delivery system for meloxicam achieved enhanced bioavailability in rats [25]. Poly-N-vinylpyrrolidone NPs loaded with indomethacin exhibited improved anti-arthritis effects in a rat paw model [26]. A NP formulation of pterostilbene demonstrated increased area under the curve (AUC) and Cmax kinetics, along with increased efficacy against acetaminophen-induced liver injury in mice compared with the free drug [27]. A nanosuspension of acetaminophen showed improved bioavailability and safety (such as liver and renal injury) compared to the conventional drug form [28].

Formulations of other drugs: Several drugs with low oral bioavailability have been formulated as NPs for oral administration including simvastatin, sulpiride, albendazole, and acyclovir. Silica-lipid hybrid formulations of simvastatin exhibited increased bioavailability in a clinical trial [29]. Prior studies have demonstrated enhanced intestinal permeation and bioavailability of NP formulations of sulpiride and albendazole [30,31]. An NP formulation for acyclovir was also shown to have significantly higher blood concentrations in rats compared to the conventional form [32].

2.3 Novel NP Formulations for IBD

IBD is a chronic and recurrent inflammatory condition that affects the GI tract, with two main subtypes being Crohn's disease (CD) and ulcerative colitis (UC) [3]. Globally, more than 6.8 million individuals suffer from CD or UC [33]. Intestinal fibrotic strictures [34,35] and perianal fistulas [36–40], feared complications develop in affected individuals. To date, there is no cure for CD and UC [41,42], but rather treatments aim at inflammation or treating complications. Previous reviews have discussed NP-based formulations for IBD [20,43–45]. Here, we review the most recent development of DDSs in this category (**Supplementary Table 1**).

Formulations for natural bioactive compounds: Several natural compounds have demonstrated effectiveness in experimental colitis, however, their poor water solubility and low membrane permeability limit their bioavailability. Innovative NP-based DDSs for these compounds have demonstrated increased efficacy in colitis models.

Two recent studies introduced novel NP formulations for oral delivery of berberine. One formulation increased the C_{max} of berberine by 2-fold, significantly relieved symptoms of dextran sulfate sodium (DSS)-induced colitis in mice compared with the free drug [46]. The other formulation released berberine in response to H_2O_2 in inflamed colon, and significantly ameliorated DSS-induced colitis in mice compared with free berberine, suggesting potential targeting of inflamed sites [47]. Other studies have shown enhanced oral bioavailability of curcumin with NP formulations. One was a curcumin-loaded self-nanoemulsifying DDS with hydroxypropyl methylcellulose as precipitation inhibitor [48] which demonstrated an increased drug Cmax by 27-fold and AUC_{0-12h} by 39-fold in rat blood compared with free curcumin. The other enhanced delivery of curcumin by targeting both CD44 and gut microbiota which resulted in prolonged residential time in the GI tract, increased bioavailability, and superior protection of DSS-induced colitis in mice compared with the free drug [49]. Additionally, novel NP formulations have increased oral bioavailability of two bioactive compounds including utilizing solid lipid NPs to deliver cinnamaldehyde [50] as well as loading tripterine to selenized polymer-lipid hybrid NPs [51]. Other NP formulations resulted in more targeted delivery, including biomimetic NPs to deliver patchouli alcohol, which targeted mouse intestinal microvascular endothelial cells *in vitro* and in the inflamed colon of DDS-induced colitis in mice [52], and silica-containing redox nanoparticle to deliver silymarin that targeted the colon [53]. Another study reported the utilization of calcium pectinate and hyaluronic acid to modify lactoferrin NPs for encapsulation of rhein [54]. The resulting formulation was stable in the GI environment and effectively targeted colon lesion sites against inflammation in DSS-induced colitis mice. Another NP formulation, comprising of antimicrobial peptide musca domestica cecropin and mesoporous carbon NPs, demonstrated good biocompatibility and significant improvement in colonic injury in DSS-colitis mice compared with the free peptide [55].

Formulations for clearance of reactive oxygen species (ROS): In IBD, there is an excess of ROS in the mucosa causing surrounding tissue damage and destruction [56]. This phenomenon promoted research efforts to develop therapies for clearance of ROS. One study demonstrated polydopamine NPs with ROS scavenging and inflammation-directed targeting properties [57]. These NPs, coupled with an antimicrobial peptide mCRAMP coated with macrophage membrane, effectively reduced the production of pro-inflammatory cytokine and increased anti-inflammatory cytokine levels both *in vitro* and in DSS-colitis mice. In another study, researchers covalently assembled casein phosphopeptide with genipin to create an

NP formulation that tolerated enzymatic degradation, accumulated at inflamed sites passively, demonstrated ROS clearance activity, and provided protection against colitis in model mice [58].

A recent study investigated an NP formulation of dexamethasone using curcumin conjugated hydroxyethyl starch as vehicles [59]. The NPs targeted inflammatory sites to release dexamethasone through degradation of hydroxyethyl starch by α-amylase that was overexpressed in the inflamed colon. The formulation demonstrated both anti-inflammatory and ROS scavenging activities, thereby effectively relieving lesions in DSS-colitis in mice. A similar strategy used mesoporous polydopamine nanoparticles to load TNF-α-siRNA for colitis treatment [60]. Rectal administration showed that the NPs passively accumulated in inflamed colon and effectively alleviated inflammation of DSS-induced colitis in mice. Another group reported a pH/ROS dual-responsive micelle NP formulation by covalently linking active quercetin to glycol chitosan (GC) using aryl boronic ester as a responsive linker. These NPs were stable in mice stomach, and oral administration of the NPs better protected DSS-induced colitis in mice compared with the free quercetin, indicating targeted drug release at inflamed sites [61].

Researchers also used biologically safe nanozymes, artificial enzymatic nanomaterials with intrinsic enzyme-like activities [62] as ROS scavengers for the treatment of UC. One study reported a formulation of carbon nanodot-superoxide dismutase (SOD) nanozyme loaded with CRISPR/Cas9 targeting CD99 [63]. The NPs targeted inflamed sites, and effectively ameliorated DSS-induced colitis in mice owing to SOD-mediated scavenging of ROS and knocking down CD99 (over expressed in UC). Another study used polyvinylpyrrolidone as carriers to construct a nanozyme. This PVP-modified nanozyme was stable in the stomach and intestine, and targeted inflamed sites in DSS-induced colitis mice in a pH-dependent manner. The nanozyme notably reduced the expression levels of proinflammatory factors, such as IL-6, IL-1β, TNF-α, and inducible nitric oxide synthase in the colitis colon in model mice compared with untreated controls, implying a mechanism of anti-inflammation [64].

Novel antifibrotic NP formulations: To date, though numerous NP formulations have been reported to target inflammation and colitis in animal models, few were designed for the treatment of intestinal fibrosis and stricture reformation in IBD. One recent study reported a nanozyme with ROS scavenging and anti-fibrotic activity *in vitro* and *in vivo* [65]. The nanozyme significantly improved colitis symptoms, reduced fibrin deposition and a-SMA expression in colitis lesions in trinitrobenzene sulfonic acid (TNBS)- and DSS-mouse models compared with untreated controls. However, the study did not include a stricture model.

Our group recently identified sulconazole (Sul) as a top antifibrotic agent from screening 1600 FDA-approved small molecules. Sul is an antifungal agent for topical use. Due to its poor water solubility, we engineered Sul as an injectable nanocrystal formulation (Sul-NC) for local application against fibrosis [8]. *In vitro*, Sul-NC achieved sustained release over two weeks and was stable in a tested period of 110 days at 4 °C (Fig. 2A, Ref. [8]). We showed that Sul-NC was highly effective in preventing skin and intestinal fibrosis in rodent models. In the skin model, Sul-NC reduced bleomycin-induced dermal thickening by 1.62 or 1.46 fold compared with vehicle control ($p < 0.05$) (Fig. 2B). In the intestine transplant model, Sul-NC decreased collagen layer thickness in intestine grafts by 2.7–3.2 fold compared with vehicle control ($p < 0.05$) (Fig. 2C). We further demonstrated in a patient-like esophageal stricture model in swine that Sul-NC was highly effective in preventing fibrosis and stricture reformation evaluated two weeks after dilation and treatment (Fig. 2D). Measurement of interior lumen diameters showed that the strictures treated with Sul-NC remained largely open (mean = 6.3 $\pm$ 1.9 mm), while the untreated strictures stayed very narrow (mean = 1.2 $\pm$ 0.9 mm) ($p < 0.05$) (Fig. 2E). Sul-NC was well-tolerated and safe in experimental animals [8]. Our data obtained support further preclinical studies to develop Sul-NC as an antifibrotic medication.

2.4 Summary

The evolution of NP-based DDSs broadens the horizons for administering therapeutics through the GI tract. This includes accommodating water-insoluble drugs, antibodies, proteins, and nucleic acids. These DDSs surmount GI barriers enabling controlled release of APIs and targeted delivery to specific sites as well as increasing bioavailability while minimizing toxicity. Despite the promising appeal of nanomedicine, a disconnection persists between animal models and their relevance to human diseases, hindering the seamless translation of NP systems into clinical medications. A further notice is that among the NP-based DDSs reviewed here, only one system designed to deliver Simvastatin (SLH-A) entered clinical trial [29].

3. Hydrogel-Based Systems for Drug Delivery in the GI Tract and the Treatment of IBD

3.1 Overview of Hydrogel Properties and Design Principles

A hydrogel is a three-dimensional polymeric network capable of absorbing and retaining a large quantity of water (typically 70–99%) while preserving its structural integrity [66]. The high-water content not only provides a physical similarity to tissues, making them tissue biocompatible, but also minimizes the risk of drug denaturation and aggregation upon exposure to organic solvents during system preparation [66]. There are several design frameworks for hy-

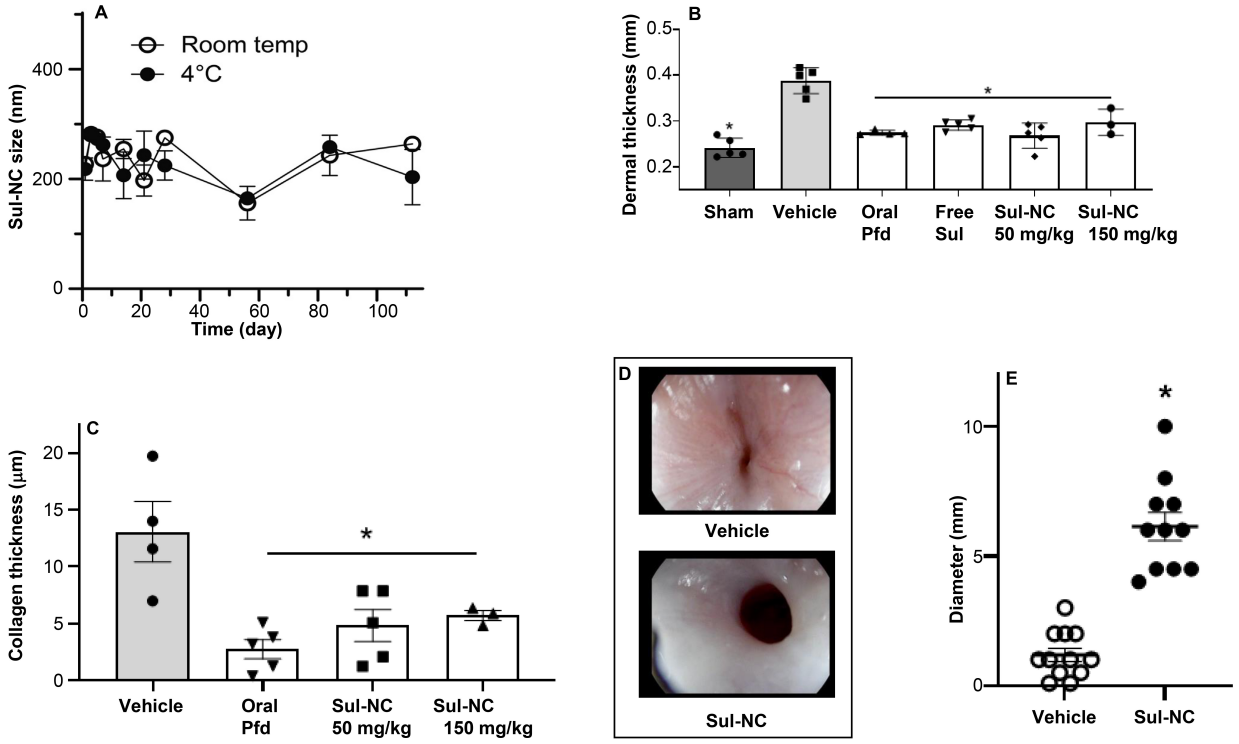

Fig. 2. Sulconazole nanoparticles (Sul-NC) developed against fibrosis in the GI tract. (A) Sul-NC is stable for 110 days tested. (B) Mouse skin model: quantification of dermal thickness from the bleomycin-induced skin fibrosis model (n = 5) after once weekly injection of Sul-NC (50 mg/kg or 150 mg/kg), IP injection of sulconazole (Free Sul, 10 mg/kg) every other day (Every 2d IP), or daily oral administration of pirfenidone (Pfd) (100 mg/kg). Mice not induced with bleomycin shown as Sham, and bleomycin with vehicle injections shown as Vehicle. Data shown as mean ± SD, $*p < 0.01$ compared to Vehicle. (C) Mouse intestine model: The collagen layer thickness in small intestine grafts was significantly decreased with the single Sul-NC injections and the daily oral pirfenidone treatment. Data shown as mean ± SEM, $*p < 0.01$ compared to untreated Control. Vehicle: PBS, Oral Pfd three times daily oral gavage with pirfenidone at 100 mg/kg for 7 days, a single injection of Sul-NC at 50 mg/kg, a single injection of Sul-NC at 150 mg/kg. (D) Swine esophageal strictures model: representative endoscopic image at two weeks post dilation of strictures, treated with the vehicle (upper), or with injection of Sul-NS at dilation (lower). (E) The luminal diameter was measured from tissue sections from pigs treated with Vehicle (n = 12 strictures from 5 pigs) or Sul-NC (n = 11 strictures from 5 pigs). Data shown as mean ± SEM. $*p < 0.05$ compared to Vehicle. Reproduced with permission from Li *et al*., Gastroenterology; published by Elsevier, 2023 [8].

drogel delivery systems, including the use of natural polymers (such as collagen and chitosan) and synthetic polymers (such as polyethylene glycol (PEG) and poly(lactic-co-glycolic acid) [66–69]. One of the main advantages of hydrogel-based DDSs is that they encapsulate and deliver a wide range of therapeutics, including small molecules, proteins, nucleic acids, and cells [66,68].

Hydrogels stand out as an appealing form of drug delivery system due to their distinct properties, including tunability, biocompatibility, and biodegradability [70]. The tunability of hydrogels allows for the modification of their physical characteristics to meet specific drug delivery requirements, such as drug loading capacity, controlled release, and release kinetics modulated by altering crosslink density and hydrogel composition [66]. There are several mechanisms of drug loading, including physical entrapment where drugs are physically trapped within the porous structure of hydrogel; diffusion-based loading where drugs diffuse into the hydrogel matrix over time; electrostatic interactions which harnesses strong electrostatic interactions to form controllable hydrogels; or chemical cross-linking in which drugs bind to the polymer chains within hydrogels [66,67,71]. The choice of drug loading mechanism depends on the properties of the hydrogel, the drug, and the targeted drug release kinetics. The mechanisms of drug release include diffusion-controlled release where drugs diffuse through the hydrogel matrix into the surrounding environment; erosion-controlled release while the hydrogel gradually degrades or erodes over time; or stimuli responsive release, such as changes in pH, temperature, or the presence of specific ions, which trigger drug release through swelling or conformational changes [66,72]. The choice of release mechanism depends on the specific therapeutic goals and the desired release kinetics for a particular application.

3.2 Novel Hydrogels for Oral Delivery of Systemic and Local Acting Drugs

Hydrogel-based DDSs present a viable option for oral administration of therapeutics, especially for substances such as proteins and nucleic acids sensitive to the harsh GI environment. Sharp *et al*. [73] comprehensively reviewed hydrogel systems for oral delivery, including formulations, polymer types, and delivery sites. Here, we present novel systems with animal studies for GI delivery, focusing on the formulations that are pH-responsive and those targeting the lower GI tract with increased efficacy (**Supplementary Table 2**).

Hydrogels responsive to pH changes: Hydrogels have been tested utilizing cargo medications from different drug categories. Baicalin is an anti-inflammatory, antioxidant, and anti-apoptotic agent for the treatment of gastric ulcers, however, low solubility limits its oral bioavailability. A research group created a pH-responsive hydrogel that could overcome this limitation and further demonstrated superior efficacy against acute and chronic gastric ulcers in rabbits compared to free baicalin [74]. Diclofenac sodium, a pain and anti-inflammatory medication, is sensitive to the GI environment and causes irritation of the stomach. The authors loaded diclofenac sodium on alginate/ZnO hydrogel nanobeads stabilized by the carboxymethyl chitosan which resulted in a slower and sustained drug release *in vitro*, and demonstrated higher oral bioavailability than conventional delivery in PK study in rats [75]. Shifting to antibiotics, colicin E9 and Ia specifically target *E. coli* colonization, but are sensitive to low pH and enzymatic inactivation in the upper GI tract. A novel microcapsule hydrogel protected colicins from such inactivation, targeted colicins to *E. coli* LF82 colonization sites in the lower GI tract, and decreased LF82 intestinal colonization in treated mice compared with controls treated with empty microcapsules [76]. Furthermore, a group of investigators developed novel hydrogel microparticles for oral delivery of insulin [77]. These particles protected insulin from degradation due to the inhibition of trypsin by the bacterial cellulose-g-poly(acrylic acid) hydrogel. They demonstrated that oral administration of insulin-loaded microparticles in a rat model of diabetes had higher efficacy and an increased bioavailability of 7.45-times compared with oral insulin solution. Hydrogels have also been used for oral delivery of vaccines. A recent study demonstrated a hydrogel system for oral delivery of ovalbumin and cholera toxin [78]. Administration of an ovalbumin-loaded hydrogel with cholera toxin to rats or cholera toxin-loaded hydrogel to mouse significantly increased the levels of anti-ovalbumin IgG and IgA, or anti-cholera toxin IgG and IgA in the plasma, respectively, compared with corresponding control solutions.

Hydrogels developed to carry poorly permeable drugs: A group of researchers developed a planar microdevice system for enhanced *in vivo* retention and oral bioavailability of poorly permeable drugs [79]. The authors engineered thin layer unidirectional releasing hydrogel microreservoirs to test a model drug acyclovir, a medication used for infections caused by the herpes simplex virus. The acyclovir-entrapped hydrogel showed enhanced drug permeation in Caco-2 monolayer compare with the free acyclovir solution. The large thin wall of the microreservoirs gave rise to enhanced epithelium retention compared with spherical microparticles. Moreover, the bioavailability of acyclovir delivered through oral gavage in mice was 4.5-folds higher compared with an oral gavage of acyclovir solution [79].

3.3 Novel Hydrogel Delivery Systems for IBD

Previous reviews have discussed hydrogel monomers, hydrogel systems, hydrogels with advanced functions such as adhesion and pH-response, as well as formulations for the treatment of IBD [69,80]. Here, we discuss the newest hydrogel systems developed for IBD (**Supplementary Table 2**).

Delivery of natural bioactive compounds: Several studies reported novel hydrogels that increased oral bioavailability of natural anti-inflammatory compounds for IBD. In one study, the investigators encapsulated magnolol into the core-shell of zein-based nanoparticles with chondroitin sulfate coating. Compared to the empty particles, magnolol loaded-NPs showed prolonged colon retention and targeted the inflammatory surface *ex vivo* and *in vivo*, and protected mice from DSS-induced colitis [81]. Another study reported a nanocomposite hydrogel synthesized from graphene oxide containing azoaromatic crosslinks and poly (vinyl alcohol) for curcumin delivery. *In vitro* and *in vivo* analyses showed that the hydrogel protected curcumin from gastric acid and intestinal enzyme inactivation, and enhanced colon delivery with prolonged residence time. The curcumin-loaded hydrogels displayed significantly higher AUC (3.15-fold) than the drug suspension, suggesting increased bioavailability [82]. A group of researchers prepared a formulation for colon delivery of 6-Shogaol (an active constituent of ginger) for the treatment of colitis where they loaded 6-Shogaol on biocompatible polymeric nanoparticles. Oral administration of these nanoparticles encapsulated in chitosan/alginate hydrogel significantly protected mice from DSS-induced colitis and accelerated wound repair [83].

Additionally, a group of researchers produced a mucoadhesive anti-inflammatory microsphere hydrogel using thiolated-hyaluronic acid. The microspheres were acid resistant and remarkably targeted the colon, thereby efficiently regulated gut immune homeostasis and optimized the composition of flora community. Both *in vitro* and *in vivo* studies showed that the microspheres inhibited pro-inflammatory cytokine production, induced type 2 macrophage differentiation, and alleviated DSS-induced colitis in mice [84].

Delivery of 5-Aminosalicylic acid (5-ASA): A recent study designed hydrogel beads for controlled release of 5-ASA in the lower GI tract to enhance its efficacy for UC. These beads were pH-responsive and released the loaded drug in the colon rather than in the upper GI tract. *In vivo* experiments showed that the hydrogel beads had enhanced efficacy against DSS-induced colitis in rats compared with the free drugs, suggesting a potential tool for colon-targeted drug delivery [85]. Similarly, to reduce the severe side effects of 5-ASA, such as headache, nausea, vomiting, loss of appetite, and pain and cramping, a group of investigators developed a colon-specific hydrogel delivery system for this drug as well as a prolonged colon retention over 12 hours. *In vivo* studies demonstrated that the 5-ASA-loaded hydrogel was more effective in controlling DSS-induced colitis in mice than conventional tablets [86].

DDS to deliver APIs to fistulas: Perianal fistulas (PAFs) are a serious complication of CD. Despite employing various medical and surgical interventions, CD-PAFs tend to exhibit resistance to treatment, with fewer than 50% showing a positive response to any therapeutic approach [42]. To develop new therapies for fistula treatment, our group has engineered a nanofiber-hydrogel composite (NHC), named mfNHC capable of loading adipose derived stem cells (ADSC) for fistula healing in model rats [87]. We fabricated the mfNHC by conjugating (poly-ε-caprolactone (PCL) fiber fragments with hyaluronic acid (HA) hydrogel (Fig. 3A, Ref. [87]). The pore size of the hydrogel ranges from 5 to 250 µm and are tunable to fit cell loading.

We examined ADSC-loaded mfNHC in a rat subcutaneous model for site retention, and observed more than 50% of the mfNHC remained at the injection site at day 28, and approximately 55% of the loaded cells were retained in the mfNHC at day 14 after injection. In addition, host cells were able to infiltrate into the mfNHC. Moreover, blood vessels were generated in the mfNHC by day 28 (Fig. 3B).

To evaluate fistula healing efficacy of the mfNHC, we created a rat model of fistulas and treated three groups of animals with ADSC-loaded mfNHC, mfNHC alone, or surgery, respectively. We demonstrated that ADSC-mfNHC produced the greatest fistula healing effect, the least inflammatory infiltrate, and the most vigorous angiogenesis and host cell infiltration (Fig. 3B,C). The effect of fistula healing can be demonstrated by reconstructing 3D volumes of fistula tracts with each treatment. The average 3D volumes were 39.18 ± 15.8 mm^3 for the surgery group (n = 6), 18.67 ± 11.16 mm^3 for the mfNHC-250 group (n = 6), and 6.57 ± 9.5 mm^3 for the ADSC-mfNHC-250 group (n = 6). Compared with the surgery group, the healing effect (volume reduction) of mfNHC-250 or ADSC-mfNHC-250 was 2.1-fold higher ($p < 0.05$) and 6-fold higher ($p < 0.01$), respectively (Fig. 3C) [87]. Furthermore, treatment with ADSC-mfNHC suppressed the expression of genes associated with inflammation and immunity, including *Ccl11*, *Ccr2*, *Ccr5*, *Ccr9*, *IFN-γ*, *IL-13*, *IL-5*, *IL-6*, and genes expressing extracellular matrix remodeling and fibrosis proteins, including *Cx3cr1*, *Cxcl12*, *Cxcr3*, *ITGB2*, *Mmp1*, *Mmp10*, *Mmp12*, *Mmp3*, and *Mmp7*. In addition, ADSC-mfNHC-250 treated fistulas exhibited fewer MPO$^+$ neutrophil cells, CD20$^+$ B cells, CD45RO$^+$ memory T cells, and CD68$^+$ macrophages in fistula areas compared with those treated with surgery. Moreover, the ADSC-mfNHC reduced the production of proinflammatory cytokines, including IFN-γ, CCL3, IL-6, TNF-α, CCL20, and IL-17, while increased anti-inflammatory cytokines such as IL-4 and IL-13.

ADSC-mfNHC accelerated fistula healing not only by physically filling the fistula, but also by stimulating host cell infiltration and blood vessel generation, reducing local inflammation and the presence of inflammatory cells, and modulating production of cytokines from helper T lymphocytes and macrophages. The ADSC-mfNHC has translational potential to clinical trials.

3.4 Summary

In summary, hydrogel-based drug delivery systems have shown great potential in the field of drug delivery. These systems offer advantages such as controlled release of drugs, enhanced drug stability, and improved bioavailability. Additionally, hydrogels can be tailored to respond to specific stimuli, allowing for targeted drug delivery. However, there are also limitations to these systems such as limited drug loading capacity and difficulty in achieving uniform drug distribution within the hydrogel matrix. Of note, none of the hydrogel-based systems reviewed here entered clinical trial. Despite these limitations, the benefits of hydrogel-based drug delivery systems make them a promising approach for improving the efficacy and safety of drug therapies.

4. Untethered Microgrippers for GI Tract Drug Delivery

4.1 Overview of Design Principles and Fabrication Techniques

Untethered microgrippers are microrobots that operate autonomously using self-powered actuation mechanisms triggered by various stimuli, such as thermochemical, magnetic, or light signals [88–90]. In this review, we use the terminology microgripper for untethered microrobots. Over the past 15 years, various microgrippers have been developed for biomedical applications since the introduction of chemically actuated microgrippers [91]. Microgrippers can be designed for gripping, holding, and releasing small objects; performing microsurgery; and even for targeted drug delivery (specifically tailored as “theragrippers”) [4,92]. Fundamental attributes of microgrippers include navigation and shape-changing capabilities which are crucial for locomotion and targeted drug delivery [93]. Reviewed elsewhere are detailed actuation mechanisms, fabrication methods, navigability *in vivo*, and specific applications [88–90].

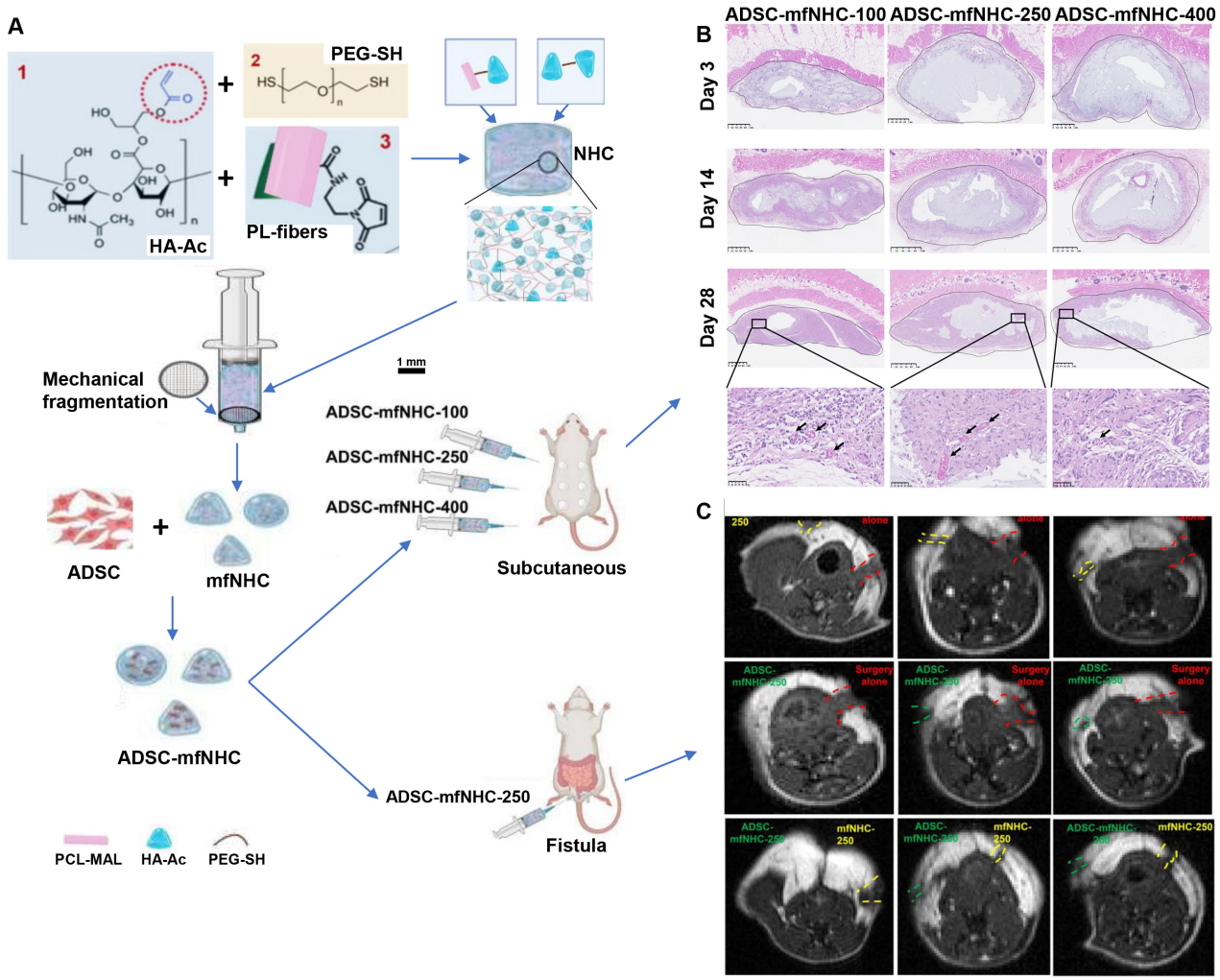

Fig. 3. Synthesis and *in vivo* studies of adipose derived stem cells (ADSC)-mfNHC. (A) Diagram illustrating the synthesis of nanofiber-hydrogel composite (NHC) and the delivery ADSC-mfNHC in a rat model of Crohn's disease-perianal fistulas (CD-PAF). (B) ADSC-mfNHC implants in a rat subcutaneous injection model: hematoxylin and eosin (H&E) staining of ADSC-mfNHC of three storage moduli at days 3, 14, and 28. The images indicate host cell infiltration and microvascular development in the implants (top scale bar, 1 mm; bottom scale bar, 50 μm). (C) ADSC-mfNHC-250 for the treatment of CD-PAF in a rat model: magnetic field (MRI) images showing that ADSC-mfNHC-250 achieves superior fistulas healing (green dashed line) compared to mfNHC-250 (yellow dashed line) and surgery at day 48 (red dashed line). Reproduced with permission from Li *et al*., Science Advances; published by the American Association for the Advancement of Science, 2023 [87].

4.2 Microgrippers for Drug Delivery in the GI Tract

Existing GI delivery systems aimed at enhancing mucosal adhesion or mucus-penetration have certain limitations, including short residency time, fast clearance, and potential obstruction [2]. Notably, even extended-release formulations frequently traverse the entire GI tract before completely dispensing their full dose of medication.

In over a decade research in the field of untethered microdevices, our group developed a series of model microgrippers with applications in the GI tract [88]. Inspired by hookworms, we recently developed a novel theragripper that could latch onto the mucosal tissue with prolonged retention time for drug release *in vivo* [4]. The theragrippers were star-shaped and had a center penal for drug loading and multiple sharp claws for effective GI mucosa latching (Fig. 4A,B, Ref. [4]). As a proof-of-concept study using ketorolac as a model drug, we administrated 2000 grippers (approximately 23 ng of ketorolac per gripper) to the colon in rats (~45 μg/animal) [4]. We demonstrated that the grippers remained in the colon for 24 hours, leading to significantly increased drug exposure and plasma concentrations compared to rats receiving the same amount of free ketorolac. We observe a 10-time drop of free ketorolac in plasma within the first 3 hours, while a comparable reduction with grippers extended up to 8 hours. Additionally, theragrippers provided sustained exposure from 8 and 18 hours af-

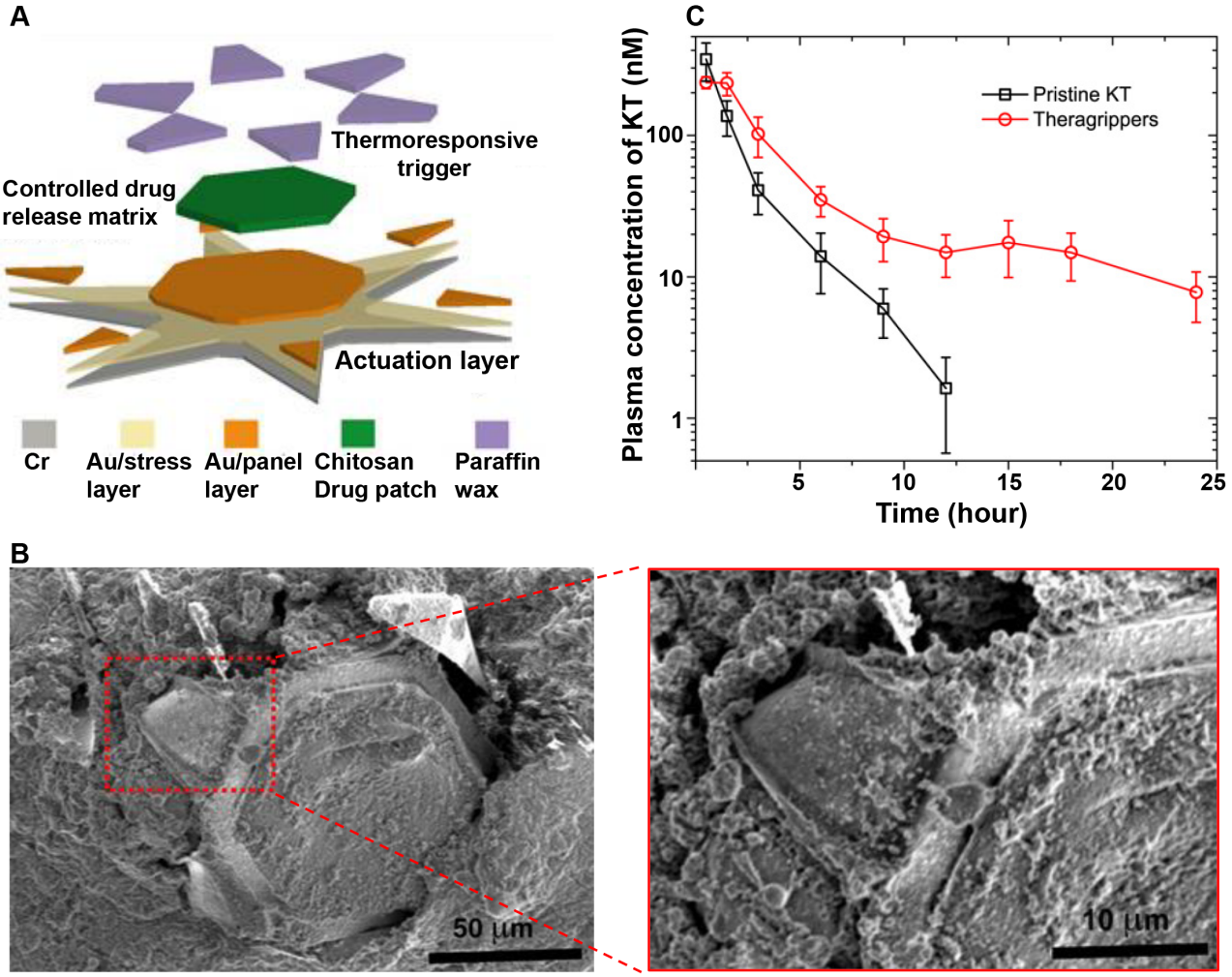

Fig. 4. Theragripper fabrication, mucosal latching *ex vivo*, and Pharmacokinetics of drug delivery *in vivo*. (A) Parallel fabrication of the theragrippers: functional block diagram illustrating the microfabrication steps for an array of theragrippers, showing the actuation layer, drug-eluting layer, and the thermoresponsive trigger. (B) Scanning electron microscopy (SEM) image of a theragripper latching onto the colon mucosa *ex vivo*. Scale bar = 50 μm (left) and 10 μm (right). (C) Theragrippers extend the delivery of ketorolac (KT) *in vivo*: plot of the plasma concentration of ketorolac measured in rats as a function of time after pristine or free drug (black) and theragripper (red) were administered intrarectally. Reproduced with permission from Ghosh *et al*., Science Advances; published by the American Association for the Advancement of Science, 2020 [4].

ter attaching to the mucosa (Fig. 4C). These results demonstrate the potential of the active, shape-changing, and self-latching theragrippers targeted sustained drug release in the GI tract.

While mucosal-latching microgrippers offer prolonged residential period and sustained drug delivery, microgrippers may require mobility to navigate in hard-to-reach and unpredictable environments. Magnetic field driven manipulation has emerged as a strong candidate for navigating microscale objects *in vivo* in the past few years [88]. Recently, our collaborator's group reported a novel type of magnetic microgripper that was guided by a clinical magnetic resonance (MR) imaging scanner [93]. The authors performed MR navigation of Fe coated microgrippers in porcine esophagus *ex vivo*, and showed that the microgrippers could be manipulated inside the porcine esophageal lumen. The combined use of a single clinical MR system for imaging, pulling, and guidance offers significant value for translation applications such as drug delivery.

4.3 Summary

In summary, the development of microgrippers for drug delivery in the GI tract, including theragrippers and magnetic microgrippers, shows potential for targeted drug delivery and extended drug release times. To date, no specific type of microgrippers for GI delivery entered clinical trial. Further research and development are needed to optimize these microgrippers for clinical applications.

Such studies may include (1) developing platforms such as oral capsules or rectal suppositories to deploy theragrippers; (2) fabricating microgrippers deliverable by magnetic field (MRI) or endoscopic guidance for precision drug delivery or tissue retrieval in different portions of the GI tract even in the bile duct; (3) enhancing biocompatibility and safety by using transient and biodegradable materials in fabrication; and (4) conducting stringent *in vivo* preclinical studies include efficacy, PK, and toxicity of delivered drugs in large animals such as swine.

5. Conclusion

As the field of drug delivery continues to advance, we can expect to see further development and optimization of systems for GI tract delivery and the treatment of IBD. With ongoing research and innovation, we may see the emergence of novel drug delivery categories that provide even greater precision and higher efficiency in drug delivery, such as the use of a programmable protein delivery system precisely targeting specific cell types [94]. Additionally, we can expect to see increased focus on biocompatibility and safety of drug delivery systems, as well as the use of personalized medicine approaches to tailor drug delivery to individual patient needs. Furthermore, we can anticipate the development of integrated systems that combine drug delivery with diagnostics and monitoring technologies for improved disease management, or systems for automatic, precise dosing. As drug delivery technologies continue to evolve and mature, we can expect to see acceleration in translation of existing as well as newly developed systems to clinical practice.

The future of gastrointestinal drug delivery maybe driven by rapid advancements in patient-centered design and technologies that enhance drug delivery specificity, precise targeting and cost-effectiveness. A key focus will be on oral formulations that transform patient experiences and disease management, as well as improve adherence.

Abbreviations

5-ASA, 5-Aminosalicylic acid; ADSC, adipose derived stem cells; API, active pharmaceutical ingredient; AUC, area under the curve; CD, Crohn's disease; Cmax, maximum serum concentration; CRISPR, Clustered regularly interspaced palindromic repeats; DDS, drug delivery systems; DSS, dextran sulfate sodium; GI, gastrointestinal; HA, hyaluronic acid; IBD, inflammatory bowel disease; IFN-g, interferon-gamma; Ig, immunoglobulin; IL, interleukin; mCRAMP, murine cathelin-related antimicrobial peptide; MPO, myeloperoxidase; NHC, nanofiber-hydrogel composite; NP, nanoparticle; PAF, perianal fistulas; PCL, poly-ε-caprolactone; PEG, polyethylene glycol; PK, pharmacokinetics; ROS, reactive oxygen species; SOD, superoxide dismutase; SOD, superoxide dismutase; TNBS, trinitrobenzene sulfonic acid; TNF-α, tumor necrosis factor-alpha; UC, ulcerative colitis; a-SMA, Alpha Smooth Muscle Actin; Ccl1, C-C Motif Chemokine Ligand 1; CCL3, C-C Motif Chemokine Ligand 3; CCL20, C-C motif chemokine ligand 20; Ccr2, C-C Motif Chemokine Receptor 2; Ccr5, C-C Motif Chemokine Receptor 5; Ccr9, C-C Motif Chemokine Receptor 9; Cx3cr1, C-X3-C Motif Chemokine Receptor 1; Cxcl12, C-X-C Motif Chemokine Ligand 12; Cxcr3, C-X-C Motif Chemokine Receptor 3; ITGB2, Integrin Subunit Beta 2; Mmp1, Matrix Metallopeptidase 1; Mmp10, Matrix Metallopeptidase 10; Mmp12, Matrix Metallopeptidase 12; Mmp3, Matrix Metallopeptidase 3; Mmp7, Matrix Metallopeptidase 7.

Author Contributions

Conceptualization, FMS; writing-draft preparation, HC; literature search and consolidation, reading, creating figures, and writing-review, revision and editing, HC, WI, JEH, LL, and FMS; supervision, FMS. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/FBL25281.

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