Smart pills for gastrointestinal diagnostics and therapy

Cummins, Gerard

DOI:
10.1016/j.addr.2021.113931

Document Version
Peer reviewed version

Citation for published version (Harvard):
Cummins, G 2021, 'Smart pills for gastrointestinal diagnostics and therapy', *Advanced Drug Delivery Reviews*, vol. 177, 113931. https://doi.org/10.1016/j.addr.2021.113931

Smart pills for gastrointestinal diagnostics and therapy

G.Cummins[1]

1. School of Engineering, University of Birmingham, Birmingham, B15 2TT, United Kingdom

Email: G.Cummins@bham.ac.uk

Abstract: *Ingestible smart pills have the potential to be a powerful clinical tool in the diagnosis and treatment of gastrointestinal disease. Though examples of this technology, such as capsule endoscopy, have been successfully translated from the lab into clinically used products, there are still numerous challenges that need to be overcome. This review gives an overview of the research being done in the area of ingestible smart pills and reports on the technical challenges in this field.*

Keywords: capsule endoscope; drug delivery capsule; smart pill; gastrointestinal diagnosis; gastrointestinal therapy; ingestible electronics

1. Introduction

Smart pills can be defined as an ingestible capsule containing electronic or mechanical elements that traverse the gastrointestinal (GI) tract for purposes ranging from diagnosis, treatment, sampling or surgery. These pills are easily swallowed by most people, thereby resulting in minimal discomfort, greater patient acceptance and can traverse the entire length of the GI tract. Diagnostically; these pills enable the use of novel sensors and imaging devices to improve our understanding of GI disease's aetiology with greater ease. From a therapeutic perspective, these devices open up the possibility of localised, targeted delivery of therapeutic agents to specific regions of the GI tract or systemic delivery of biologics through transepithelial delivery. The minimally invasive nature of these devices enable areas of the GI tract, such as the small intestine, to be sampled with relative ease compared to more invasive methods.

Though smart pills capable of gastric pH monitoring were first reported as far back as 1965 [1] and simple devices and smart pills for drug absorption studies along the GI tract were reported in 1961 and 1982, respectively [2] [3], it is arguably the introduction of the capsule endoscope (CE) in 2000 [4,5] that has lead to the increase in the number of smart pills reported in recent years [6]. The CE enabled inspection of the small bowel, which was not easily accessible by conventional endoscopy. However, CE remains the most widely used smart pill

in clinical practice despite the increased research activity in smart pills. The limitations of the CE as a diagnostic technology are increasingly understood due to its reliance on a single imaging modality, limiting clinical diagnosis to superficial changes in the appearance of the mucosal surface [6]. The detection of obscure GI bleeding in the small bowel is the primary recommended clinical use of these devices [7]. Integrating additional diagnostic and therapeutic modalities has the potential to improve the clinical usefulness of smart pill technology. This is exemplified by the increasing number of capsules reported in the literature in recent years. These capsules can act as a platform to better our understanding of gastrointestinal pathophysiology, provide new means of gastrointestinal and systemic therapeutic delivery, and collect tissue and other samples for subsequent analysis in a minimally invasive manner This review paper will provide an overview of current progress in this field by summarising key trends in smart pill technology. The majority of the smart pills discussed in this paper have made some progress towards clinical translation. The paper structure mirrors the three areas where these capsules are being developed for according to trends in the literature, which are diagnostic, therapeutic and sampling smart pills.

2. Smart Pills for Diagnosis

Various smart pills have been proposed over the years to improve the diagnosis of GI disease and improve the understanding of its causation. These diagnostic smart pills can be divided into those that either utilises imaging technology such as optical, autofluorescent imaging, or utilises sensors to detect physical changes in the GI environment, whether pressure, pH or chemical analytes. Most of the pills described in this section are in early development, with their clinical efficacy yet to be established and technical challenges still to be solved before being clinically used.

2.1. Imaging

Capsule endoscopes rely on optical imaging of the mucosal surface to detect GI pathologies using visible wavelengths of light. These silver oxide battery-powered capsules consist of an

imaging device such as a camera, light-emitting diodes for illumination, some onboard microprocessor, and telemetry to send images to an external receiver for later analysis. The CEs may vary in the cameras' frame rate to acquire enough images within specific regions of the GI tract where transmit may be quick, such as the oesophagus or slower, such as the colon. They may also have more than one camera, as seen in the colon imaging CEs. The CEs may also vary in their useful lifetime, with battery life ranging between 0.5 to 15 hours. Since their original development by Given Imaging, several companies are now developing these devices, as shown in Table *1* . A small number of studies comparing these devices have shown no significant difference between the different CEs now available [8–10]. However, the reliance of these devices on just imaging using visible wavelengths restricts diagnosis to non-specific changes in the mucosal surface's appearance [11,12].

Other attempts at developing smart pills that image have primarily focussed on the miniaturisation and integration of modalities in clinical use, such as autofluorescent imaging [13], ultrasound [14,15] or x-ray imaging [16], some of which are shown in Figure 1. However, some capsules have also integrated imaging technologies such as optical coherence tomography (OCT) [17,18]. These activities are partially in response to current CE's limitation to mucosal imaging as technologies such as ultrasound, x-ray imaging, and OCT are capable of sub-mucosal imaging.

Autofluorescence imaging illuminates tissue with short wavelengths of light (380-500 nm) to excite endogenous or exogenous fluorophores; absorption of the incident light by the fluorophores causes them to emit light at longer wavelengths (490-590 nm). This principle allows the differentiation between malignant and benign tissue to occur easily due to reduced emission from malignant tissue [19]. This imaging technology has been widely used with conventional endoscopy. However, only one group has sufficiently miniaturised the technology to fit within a smart pill due to the use of single-photon avalanche diode (SPAD) imaging arrays, capable of detecting a single photon of light, giving a sensitivity of 19 pW/cm^2 using a 10 ms exposure time that is capable of measuring 20 μM of exogenous fluorophores such as

fluorescein isothiocyanate labelling solution and 12.5 μM of endogenous fluorophores such as flavin adenine dinucleotide. However, the imaging resolution of this autofluorescent imaging pill is not explicitly stated. Though this capsule has yet to undergo *in-vivo* trials, as the capsule is 16 mm in diameter and 48mm in length, it is larger than most other smart pills, suggesting that further miniaturisation is required to ensure safe transit through the GI tract [13].

Endoscopic ultrasonography is also clinically accepted and in routine clinical use. The miniaturisation of this technology to fit within a capsule has been a goal of several groups. Though this technology is still in its infancy, several smart pills capable of ultrasound imaging have been reported based on different technological approaches [14,15,20,21], which are summarised in Table *2*. The Khuri-Yakub group at Stanford University, USA, are attempting to produce an ultrasound imaging capsule incorporating a multi-element ring array to generate a 360^{o} image of the intestinal wall [20]. This technology employs an ultrasound frequency of 5 MHz, which would be most suitable for imaging the organs located beyond the GI tract due to the greater penetration depth and lower spatial resolution achievable at those frequencies. This technology has yet to be integrated into a capsule or tested *in-vivo*. The UK's Sonopill project focused on single-element transducers operating at frequencies as high as 30 MHz. This high-resolution ultrasound sacrifices penetration depth for greater spatial resolution capable of imaging subsurface features such as structural and tissue composition. However, it should be noted that the penetration is sufficient to enable the imaging of the intestinal wall at a resolution sufficient to distinguish each of the tissue layers in the small bowel. This transducer was used in the production of a tethered ultrasound imaging smart pill that was shown to be capable of acquiring detailed images of a porcine small bowel during *in-vivo* tests [15]. This work was subsequently used to develop a magnetically actuated capsule capable of optical and ultrasound imaging [22]. However, the capsule could not image the small bowel radially in both cases. Subsequent ultrasound imaging capsules developed by Qiu [21] and Lee [23] achieved radial imaging of the wall of the small intestine through mechanical rotation of 30 MHz and 10 MHz transducers, respectively. The resolution of the Qiu capsule, which

utilised the same frequency as the Sonopill transducer, was measured using a wire phantom to have a -6 dB axial and lateral spatial resolution of 69 and 262.5 μm, respectively [21]. The Lee capsule was measured to have a -6 dB axial and lateral spatial resolution of 300 and 680 μm, respectively [23]. For the Qiu [21], Lee [23] and Sonopill [15] capsules, the bowel was prepared by placing the animal on a liquid diet or fasting for a period before insertion to ensure optimal imaging conditions [24], which is analogous to some of the clinical protocols used to before capsule endoscopy [25]. All trials were conducted in oesphagus or small bowel, where the use of a saline drip [15], relative dimensions of the capsule to the small bowel or oesophageal diameter [15] or the presence of peristasis [23] contributed to a good coupling between the transducer and the tissue. Good coupling was assured for the magnetically actuated capsule in the large intestine due to the ability to tilt and press the capsule against tissue due to the magnetic control system [22]. As noted by Lee [23], if the lumen dimensions are larger than that of the pill, there is a risk that the pill will tumble and only make intermittent or limited contact with tissue, adversely affecting these pills ability to continuously image the GI tract. This suggests that without the use of magnetic control systems, ultrasound imaging pills may be of limited value in the stomach or large intestine. It is worth noting that the ultrasound imaging capsules tested *in vivo* to date have all been tethered; this removed the need for all the capsule systems, such as power and communications, to fit onboard the pill. Many of those systems were located off the capsule, at the other end of the tether, as the focus of the studies conducted with the tethered devices was primarily to assess the quality of images obtained from capsule-based imaging. Further work is needed to miniaturise all the capsule systems to integrate them into the pill volume before a wireless ultrasound imaging smart pill can be created.

The C-Scan system (Check-Cap, Isfiya, Israel) is a X-ray imaging smart pill that uses a short-lived radioisotope ^{191}Os, with a half-life of 15.4 days transmurally images the colon after ingestion of an iodine-based contrast agent [16,26]. The emitted 65–75 keV X-rays are divided into three rotating beams, enabling a radial view of the colon wall. Images are reconstructed

from measuring the low energy X-ray fluorescence (27 keV) produced by the interaction between photons emitted from the radioisotope and the ingested contrast agent, as well as the Compton scattering of the photons at 52–60 keV. The capsule was measured to have a longitudinal resolution of 2-3 mm and a rotational resolution of 20-25^{O}; this was deemed sufficient to detect polyps greater in size than 6 mm [26]. Though a number of *in vivo* trials have been conducted with the C-Scan system demonstrating its safety [16] and its clinical potential [27,28], further validation and direct comparison of the system with standard colonoscopy is required [16].

Optical coherence tomography is a sub-mucosal imaging technique capable of high spatial resolution comparable to conventional histological analysis of excised biopsy tissue (10 μm axial and 30 μm lateral resolution). It operates by measuring the time delay and intensity of backscattered or back-reflected light from an optical beam scanned across the sample surface [29]. High sensitivity (90.0%) and specificity (83.3%), sufficient to differentiate between Crohn's disease and ulcerative colitis, have been achieved with colonoscopically delivered OCT, demonstrating its potential for the diagnosis of inflammatory bowel disease [30]. Attempts to integrate OCT into smart pills resulted in two tethered devices primarily demonstrated in the oesophagus [17,18]. Both pills rely on an external light source that transmits light to optics integrated within the pill via an optical fibre within the tether and mechanical scanning to generate the image. The tethered capsule developed by Gora et al. was 12.8 mm in diameter and 24.8 mm long with side-viewing OCT capable of generating radial images at 20 frames per second with 30 μm lateral and 7 μm axial resolution in humans [17]. Though manual pullback of the device facilitates rapid imaging for screening purposes, it may not be sufficient to provide the stability or repeatability needed for volumetric OCT [18]. The 12 mm diameter and ~35 mm long device, produced by Liang et al. [18], were shown to generate volumetric OCT in porcine models. The ability to achieve volumetric OCT was due to an integrated longitudinal scanning system that could track non-uniformities along the scan trajectory, enabling compensation in post-processing. However, the tether used made the

smooth movement of the capsule at a constant velocity during manual pullback difficult. Significant work is required to create a fully integrated, tetherless OCT imaging smart pill that can provide clear, high-resolution images even when subject to peristaltic and other GI forces.

2.2. Physical Sensing

Changes in the physical environment of the GI tract may be symptomatic of an underlying condition. Several pills have been created to detect changes in pressure, temperature and pH. Many smart pills capable of measuring one or more of these measurands are commercially available and used as medical devices.

2.2.1. Pressure Sensing

Changes in the GI system's physical parameters may indicate a pathological condition. This is especially true for bowel motility changes, which are associated with 40% of GI conditions resulting in abdominal discomfort, pain and altered bowel habits [31,32]. Current methods of assessing bowel motility can include the endoscopic insertion of manometers, which can be uncomfortable for patients and precludes investigation of the small intestine. These limitations have led to the development of several smart pills capable of measuring pressure [33–36]. Since 2006, the SmartPill is the only wireless CE device with pressure-sensing capabilities currently on the market with FDA approval [33]. SmartPill contains a temperature sensor (25–49^{O}C), a pH sensor (pH 0.05-9.0), a single pressure sensor with an operating range 0–46 kPa and a sensitivity of ±0.650 kPa that can record the pressure of its environment. This capsule is primarily used in motility studies to measure the transit time between different regions of the GI tract based on changes in pH and pressure.

The single pressure sensor in this capsule can only measure the intraluminal pressure and not the contractile pressure due to peristalsis, both of which can be measured using conventional high-resolution manometry. Wireless pressure sensing capsules developed by Benjamin Terry’s group can measure the contractile and intraluminal pressures by using two orthogonally aligned sensors with a resolution of 0.0036 kPa [34]. Subsequent pressure

sensing capsules reported to date have only been capable of intraluminal pressure measurement [35,36] despite the clinical advantage of full pressure measurement in assessing GI dysmotility.

2.2.2. Temperature Sensing

The ability of the human body to regulate its internal temperature when exposed to a wide range of environments or increased physical activity is vital for ensuring optimal health. However, under certain conditions, internal body temperature can deviate from the optimal core temperature of $37^{O}C$ to such an extent that it can result in either fatal heat stroke due to prolonged physical exertion [37] or high ambient temperatures or hypothermia due to extreme frigidity.

Several temperature sensing capsules are available from companies such as CorTemp (HQ Inc, FL, USA) [38], Vitalsense (Equivital, NY, USA) [39], e-Celsius (BodyCAP, Herouville-Saint Clair, France) [40] and MyTemp (MyTemp, Nijmegen, Netherlands) [41]. These devices are primarily used to monitor athletes' core temperature during training and are generally not used to diagnose GI disease due to the non-specific nature of temperature as a biomarker. The temperature sensor integrated into the Smartpill is also not used for the diagnosis of GI disease; this sensor is primarily used to detect excretion of the device.

2.2.3. pH Sensing

pH sensing capsules were one of the earliest ingestible capsules developed, with the Heidelberg pH sensing capsule first reported in 1965 [1]. The Heidelberg capsule consisted of a pH-sensitive RF antenna encased in an inert plastic shell of 7 mm diameter and 20 mm length. The sensor has a ± 0.5 pH accuracy and measures within the range of 1 to 9 pH. It has been widely used in clinical studies as a minimally invasive means of accurately measuring GI pH and transit time[42].

The SmartPill capsule from Medtronic, first approved for use by the FDA in 2006, also utilises an integrated pH sensor to identify transit along the GI tract by the associated changes in pH.

The sensor is capable of measuring pH in the range of 0.05 to 9.0 with an accuracy of ± 0.5 pH [43]. This, coupled with the pressure sensing capability above, is utilised to assess dysmotility along the GI tract. These pills have rarely been used to identify GI disease other than GI dysmotility. Other groups have also created pH sensing capsules using varying approaches despite the limited clinical use of single modality pH sensing capsules [44]. Another commercially available pH sensing capsule is the wireless BRAVO capsule, also from Medtronic, which is designed to detect gastroesophageal reflux disease by recording oesophagal pH for up to 96 hours when temporarily attached to the oesophagal wall [45]. Likewise, the previously available Intellicap capsule (Philips, Eindhoven, Netherlands, widely used for drug delivery) was also capable of detecting pH to determine whether it was in the correct region of the GI tract to empty its drug reservoir [46].

2.3. Chemical and Biological Sensing

Changes in the chemical and biological composition of the GI tract can provide an objective means of confirming normal biologic processes or identifying and quantifying the response to pathophysiological or pharmacological responses to disease or therapy, respectively. The ability to sense these chemical or biological changes has the potential to improve diagnosis, stratify patients, reduce healthcare costs, expedite drug development and monitor therapeutic efficacy. Several smart pills have been created that are capable of detecting such changes.

2.3.1. Haemoglobin and other Soluble Biomarkers

Multiple biomarkers within the GI tract are commonly examined to detect GI diseases such as colorectal cancer or IBD [47]. Attempts to detect these biomarkers in-situ using a smart pill have been limited compared to the number of smart pills developed to measure physical changes. Most chemical sensing smart pills to date have focussed on the detection of soluble biomarkers such as haemoglobin due to its association with GI bleeding [48–50]. These pills primarily utilise optical sensing enabling non-contact detection of the analyte.

Conventional WLI CE can be used to identify blood in the stomach, but it cannot easily differentiate between past and active GI bleeding in the stomach. Qiao demonstrated a colourimetric detection pill that used a hue–saturation light colour detection method on blood cells selectively channelled into a measurement chamber [49]. This chamber included white LEDs for illumination, a colour sensor and an adsorptive colour-sensitive film that undergoes a change from white to red in the presence of haemoglobin. *In vitro* trials with different blood concentrations showed that the system could measure haemoglobin concentrations as low as 2.375 mg per ml, which is reported to be less than that found in areas of GI bleeding. Nemiroski also developed a smart pill to detect GI bleeding [48]. Similar to an earlier *in vivo* demonstration by members of that group [51], the Nemiroski wireless, battery-powered pill detects active bleeding through the intravenous injection of fluorescein, a FDA compliant fluorescent contrast agent whose spectra (absorption peak at 494 nm, emission peak at 512 nm) does not overlap with that of gastric juices (absorption peak at 288 nm; emission peak at 350 nm). Fluorescein emits light in the presence of blood, acting as a proxy biomarker for the detection of active bleeding in the stomach. Benchtop tests have demonstrated that the system can detect concentrations of fluorescein as low as 20 nM. However, the system's performance varies with the pH of the stomach as the spectral properties and quantum yield of fluorescein shift with pH, which can be problematic after the patient ingests water. No further work has been published on this pill.

Another pill developed to detect active bleeding is the commercially available HemoPill [50] (OVESCO, Tuebingen, Germany). This battery-powered pill of length 26.3 mm and diameter 7 mm, contains an optical sensor to measure the optical absorption at 415 nm between an LED and a photodetector placed within a recessed channel on the pill's surface [52]. At this wavelength, optical transmission through blood is at a minimum and is three orders of magnitude less than transmission at a reference wavelength (720 nm). The optical sensor can detect haemoglobin by measuring the relative change in absorption at 415 nm to the reference signal at 720 nm. Preliminary *in vivo* tests using human volunteers have been conducted [53].

Initial tests were performed on a healthy volunteer with simulated GI bleeding under various conditions through periodic ingestion of 20 ml blood. The results were compared with baseline readings from the same volunteer under the same conditions without blood intake. The capsule successfully detected simulated GI bleeding after each ingestion of blood, with the detection algorithm showing a correlation ($R^2 = 0.9016$) between changing sensor signal within 10 min of capsule ingestion and increased gastric blood concentration.

Synthetic biology was used to create a series of chemiluminescent bacteria that resided within an electronic smart pill to enable the optical detection of heme, a molecule associated with bleeding and thiosulfate, a biomarker of gut inflammation and acyl-homoserine lactone, a biomarker of infectious bacteria [54]. The pill was successfully used to detect bleeding during *in vivo* trials conducted using porcine animal models.

Other methods of detection besides optical sensing of analytes have also been attempted [55]. *In vitro* tests with an electrochemical sensing capsule that was tested using simulated intestinal fluid [55]. However, the response of these sensors was found to drift with time partially due to the adsorption of organic matter onto the electrode surface [55].

2.3.2. Gaseous Biomarkers

In addition to the detection of soluble biomarkers, smart pills have also been created to detect gaseous biomarkers associated with the metabolic activity of the microbiome [56] [57]. Kalantar-Zadeh et al. developed a wireless electronic pill that successfully demonstrated real-time measurements of hydrogen, carbon dioxide and oxygen gas levels along the GI tract in five human volunteers [57]. The 9.8 mm diameter, 26 mm long capsules included a non-specific, semiconducting metal oxide sensor responsive to all oxidising gases under aerobic and anaerobic conditions that were calibrated to detect hydrogen, carbon dioxide and oxygen. Intestinal gas entered the capsule through a semi-permeable membrane containing embedded nanoparticles that excluded water. The pill was shown to be capable of some localisation by monitoring changing oxygen concentration along the GI tract. Also, measuring

the changing levels of hydrogen provided a means of understanding the GI tract's microbial fermentation. However, the correlation of the changing levels of gas with diet types and faecal microbiomes of the volunteers using the pill were inconclusive. This research was subsequently commercialised and is now available from Atmo Biosciences [58] and undergoing trials to assess whether it can be used to diagnose irritable bowel syndrome [59].

2.3.3. Biological Sensing

A smart pill for detecting small intestinal bacterial overgrowth was recently proposed by Progenity Inc. (San Diego, CA, USA) [60]. The capsule is reported to be able to detect via optical means when it is in the jejunum and can sample the surrounding intestinal fluid in this region by opening a valve on the radial surface of the capsule, exposing a wick that is used to drive fluid into an internal sponge. An integrated fluorescence-based assay measures the sponge's changing optical properties caused by viable bacteria and sends the signal to the clinician. To date, the various subsystems of the capsule have been tested, and *ex vivo* tests are currently underway in an ongoing prospective human clinical trial.

3. Future Directions of Diagnostic Smart Pills

The increasing variety of sensors and imaging technologies integrated into smart pills could potentially open up diagnostic possibilities and overcome the limitations associated with CE. However, many of these technologies are immature and require further development and more extensive clinical trials to ascertain their clinical efficacy. Further development of smart pills with the capability to sense clinically established biomarkers of disease, coupled with improvements in accurately determining the position of the pill within the GI tract with greater resolution [61,62], would open up the possibility of detecting the site of GI disease for subsequent surgical or therapeutic targeting. However, the development of chemical sensors that can withstand the challenging GI environment is not trivial.

In addition to developing the sensors themselves and assessing their clinical efficacy, it may be that no one sensor working in isolation is sufficient to provide the accuracy, sensitivity, and

specificity demanded of clinical diagnosis. Further work may be needed to identify which combination of sensors would be needed to aid in diagnosing different pathologies. Such multi-modal pills will have implications for the integration, miniaturisation and power consumption of sensors and other onboard electronic systems. The production of increased data from these pills also has implications for communications bandwidth and clinician time, with current CE devices capable of generating 6 frames per second and hence produce thousands of images during the time they travel the GI tract. This can lead to clinicians spending 0.5-1.0 hours for a single human reader using high-speed reading techniques [63], leading to 6-20% of missed pathology occurrences [64–66]. Pills with multiple sensors or imagers will further exacerbate this problem, though the development of artificial intelligence algorithms suited to identifying a wide variety of pathologies may lessen this burden [67,68].

4. Smart Pills for Therapy

Smart pills have been used to administer or support various therapies, such as the targeted delivery of small molecules, transepithelial delivery of biologics, provision of non-pharmaceutical therapies and monitoring of adherence to the therapeutic regimen. The design of these smart pills varies depending on the specific application.

4.1. Drug Delivery and Drug Formulation

The use of smart pills for aiding the formulation of pharmaceutical agents or their delivery to the site of GI pathology has been the subject of much research. To date, most of these pills have been for the delivery or assessing the formulation of small-molecule drugs. The specifications of several of these pills have been summarised for ease of comparison in Table *3*.

The use of these smart pills for drug formulation studies enables gathering detailed and realistic information regarding how well a specific drug formulation is absorbed from key areas of the GI tract. This would facilitate a reduction in the delays encountered during Phase 1 clinical trials due to the trial and error approach used to assess multiple drug formulations [3]

and removes the need for invasive perfusion or intubation based techniques [69,70]. The advantages of using smart pills for drug delivery is well understood, as targeting diseased tissue is currently challenging, necessitating systemic treatment and consequently system-wide side-effects. The utilisation of drug-device combinations, specifically drug delivery capsules with integrated sensing or imaging capabilities, offers a means of potentially detecting and treating diseased GI tissue simultaneously, allowing targeted therapeutics and lower side effects in patients. Additionally, such capsules also open up the possibility of using minimised but localised doses of effective treatments that are generally not used due to their toxic systemic side effects.

These therapeutic smart pills generally operate on the same principle by either diffusing or expelling the active pharmaceutical ingredient (API) from an internal reservoir into the surrounding GI fluid upon detecting some form of an environmental or external trigger. Smart pills that utilise diffusion to release the API are deemed as using passive drug delivery mechanisms, while those that expel the API from the capsule are referred to as using an active drug delivery mechanism [71][72]. Whether the capsule uses passive or active delivery, most smart pills are currently passively propelled through the GI tract by peristaltic forces and eventually excreted with little control of their position or velocity at any given time. Due to this passive locomotion, drug delivery with these capsules within the small intestine can be challenging due to the fast transit time and lack of retention or anchoring mechanism.

4.1.1. Passive Drug Delivery

Due to the reliance of passive drug delivery capsules on diffusion to empty the capsules, the drug delivery rate is dependent on the diffusion rate of the drug in the environment.

One of the first passive pills to be widely used was the HF-Capsule [73–75]; as shown in Figure 2B, the capsule consisted of a 28 mm x 12 mm capsule, with an internal drug reservoir made from a latex balloon with a maximum volume of 1 ml. An oscillating circuit in the other water-resistant half of the capsule absorbs energy from an externally supplied 27 MHz RF

signal, causing a wire to heat up and melt a nylon thread that holds a spring attached to a needle under tension. When the thread melts, the spring is released and causes the needle to displace and puncture the latex balloon reservoir [76]. This balloon mechanism was prone to incomplete emptying and was challenging to fill with powders [3,77]

Another smart pill also used for the study of pharmacokinetics is the InteliSite Companion Capsule (Innovative Devices, Raleigh, NC, USA), which is shown in Figure 2D, that was developed due to challenges regarding the usage of the earlier HF capsule outside of Europe and to be used in conjunction with gamma scintigraphy [78]. An earlier version of the InteliSite device consisted of a 10 mm x 35 mm plastic capsule contains and 0.8 ml internal drug reservoir. The capsule contents are released when externally triggered by an RF signal, which causes integrated resistors to begin to heat up. The thermal energy is dissipated to shape memory alloy metal wires that straighten up at $40^{O}C$, generating a mechanical force. This force causes the inner sleeve of the capsule to rotate, aligning ports located on the inner and outer sleeves and releasing the drug via diffusion. Later InteliSite devices changed the mode of operation [79]; the capsule contained an outer sleeve and inner sleeve. The inner sleeve was removable and mounted on a spring. The inner sleeve was held in place by a cap kept in place by shape memory allow wires. The heating of these wires was again triggered by an external RF source, causing the cap to be released and the inner cage-like sleeve containing the drug to be released. However, the InteliSite capsule was known for being susceptible to gradual, preactivation leakage of liquid formulations due to a poor seal between the inner and outer sleeves and the energy required to heat the shape memory alloy wires resulted in activation times of 2 minutes or greater depending on the depth of the capsule within the body [77].

4.1.2. Active Drug Delivery

In 1961, a 16mm x 8mm stainless steel cylinder sealed with wax developed by Smith Kline and French was used to assess salyicate absorption in different parts of a canine GI tract [2]. A cross-sectional view of this capsule is shown in Figure 2A. The canine was placed inside a

large induction heating coil, which caused the ingested metal capsule to heat up and melt the wax, which released a mechanical spring used to expel the drug contents into the GI tract. The process of heating the cylinder took 3 minutes, with the temperature rising to 59^{O}C and falling back to normal in 2 to 5 minutes. Besides the high temperature and long activation times, another disadvantage of this method is that the subject must be placed within a bulky inductive heating coil for it to be used.

Another early demonstration of smart pills capable of active delivery were created by Groening at the Institute of Pharmaceutical Technology and Biopharmaceutics in Münster, Germany, an example of which is shown in Figure 2C. These capsules primarily expelled the drug via pistons pushed by gas created by electrolysis initiated by an external electrical signal [72][80][81]. The final version of this capsule created in 2007 was 28 mm x 8.5 mm in size, capable of storing 0.17 ml of drug payload [81]. However, the potential of these capsules was only demonstrated by benchtop experiments.

One of the more widely used capsules currently used in the pharmaceutical industry is the Enterion capsule (Quotient Clinical, Nottingham, UK) [3] as it enables the assessment of drug absorption in the GI tract [82–84]. This 32 mm long capsule, shown in Figure 2F, contains an internal reservoir capable of storing up to 1 ml of the formulation. The reservoir is accessed via a 9 mm diameter port that is sealed before ingestion through the use of a push on cap with a silicone O-ring seal. A separate sealed compartment also exists to allow a radioactive marker to be emitted during passage through the GI tract to identify the location of the capsule using gamma scintigraphy. Drug release is triggered by switching on a low MHz oscillating magnetic field that induces power in a tuned coil embedded within the capsule. The induced power, approximately a few tenths of a Watt, is used to heat a small (< 1 mm^3) heater rapidly in another sealed compartment behind a piston. The heater generates a rapid temperature rise that breaks a high tensile strength polymer filament used to restrain a coiled spring. Once the filament breaks, the spring pushes the piston forward, forcing the contents of the drug reservoir forward. This increases the pressure against the push-on cap, which eventually is

forced off, and the contents of the drug reservoir are ejected into the surrounding GI fluid within seconds.

The Intellicap (Medimetrics, Eindhoven, Netherlands) contained a 0.3 ml internal drug reservoir within a 27 mm x 11 mm plastic shell [46,85–88]. In this capsule, the drug was forced out of vents on the side of the capsule through the actions of the internal stepper motor. The capsule had a level of flexibility not seen in other capsules in that various release profiles could be programmed, enabling continuous release profiles of various speeds and intermittent release (single or dual burst profiles). The type of release profile was limited only by the 48-hour battery life and the minimum release time of 10 minutes. Another innovation with this capsule is that it could operate either autonomously based on input from the integrated temperature or pH sensors or a timed delay or remotely by an operator triggered RF signal. The pH sensor enables detection of the position in the GI tract removing the need for integrating radioisotopes for tracking as in the Enterion capsule or external imaging technology.

The Enterion and Intellicap are no longer commercially available. However, the SmartTab (Veloce, Denver, CO, USA) is a new commercial product currently undergoing trials that actively deliver drugs using a smart pill actuated by a smart polymer mechanism [89].

4.2. Drug Delivery Capsules for Biologics

While the drug capsules previously described can be used to deliver biologics to the small intestine, they do not offer a solution to the many challenges affecting the bioavailability of these agents. Biologics are still susceptible to enzymatic degradation, adverse pH conditions, microbiota, mucus barriers, difficulty in crossing the epithelial barrier and rapid transport through areas of high absorptive flux [90,91]. Various combined drug-delivery system solutions have been proposed to overcome many of these challenges, many of which can be grouped by their approach. Those that utilise a smart pill form factor can be loosely grouped

as achieving this via either epithelial penetration or increasing epithelial permeability, some of which are shown in Figure 3 and summarised in Table *4*.

4.2.1. Epithelial Penetration

The only method being investigated for the delivery of biologics via epithelial penetration is through the use of microneedles. While transdermal drug delivery has been the focus of most research to date concerning the use of microneedles [92,93], there have been some investigations on their use for oral drug delivery [94–97]. Various materials, such as metal [94], sugars [98] and polymers [95] have been investigated. Epithelial penetration using microneedles is an attractive solution due to the fact that studies of GI injection for therapeutic delivery have shown a quicker pharmacokinetic response compared to subcutaneous injection [94]. The time to hypoglycaemic onset, defined as a drop in the initial blood-glucose ≥5%, when 10 units of rapid-acting insulin in 1 ml of 0.9% saline were administered using a 25G needle in 75-80 kg Yorkshire pigs were measured to be 23.08 ± 7.00, 6.28 ± 4.48, 6.66 ± 1.65, and 16.91± 6.39 min for subcutaneous, gastric, duodenal, and colonic administration, respectively [94]. Another advantage of epithelial penetration via microneedles is the lack of sharp pain receptors along the intestine, enabling painless delivery of therapeutics.

With regards to safety, the height of microneedles rarely exceeds 0.2 cm [99], which is less than the 3-16 cm size range of ingested objects requiring surgical removal due to the risk to the individual's health [100]. Additionally, the administration of drugs in the GI tract via injection is a routine part of many treatments for conditions such as bleeding ulcers and polypectomy [101–103]. However, few studies have been performed on the effect of repeated or prolonged usage of microneedles on the GI tract. Studies performed with transdermal microneedles suggest that some microneedles may induce temporary and minimal inflammation around the insertion site [104]; similar studies have yet to be performed on the intestinal epithelium to determine whether a similar response is observed. While microneedles are a relatively safe way of penetrating the epithelium than other alternatives, further studies would be welcome to clarify the optimal and safest way of using this technology.

The force at which the microneedle is inserted also has implications for the safety of this method. The thickness of the small intestine varies between 3 – 5 mm, so the risk of tissue perforation must also be characterised as a function of injection force. Various grades of hypodermic needles were inserted into *ex vivo* human and porcine tissue and *in vivo* porcine tissue at different forces [95]. As expected, these experiments demonstrated that the penetration of the needles into the tissue was a function of the applied force, needle dimensions and tissue type. Force measurements showed that a force of as low as 5 mN was sufficient for needle insertion into tissue, while forces of 0.2 – 0.3 N were capable of penetrating 6 mm into *in vivo* porcine intestinal tissue. Control of the injection force and limitations on the microneedle height would also be required to mitigate the risk of tissue perforation.

The Langer Group demonstrated that capsule-based microneedle devices could be ingested and excreted without perforating the intestine or retention using a capsule that is 20 mm in length and 10 mm in diameter with an unknown number of 25G hollow needles arranged in a radial pattern protruding 5 mm from the capsule surface, this capsule is shown in Figure *3*A [94]. However, this design is limited in that penetration of the mucosa and the subsequent release of insulin is reliant on the peristaltic compression of this capsule by the small intestine. The pressure exerted by the surrounding tissue on the capsule will vary from patient to patient [105]. Additionally, the presence of chyme will also affect the microneedle penetration. This potential variability in the number of microneedles penetrating the mucosa and the depth of penetration from pill to pill will affect dosage reliability.

Later polymer microneedle based devices developed by the same group have overcome this limitation by developing devices that exert a mechanical force against the intestinal mucosa [95]. The device, shown in Figure *3*B and C, consisted of an outer cylindrical tube of 30 mm length and 9 mm diameter that was coated in a poly (methacrylic acid co-ethyl acrylate) coating that dissolved at a pH of ≥ 5.5. The inside of the tube contained a compressed steel spring encapsulated in a polyethylene glycol (PEG) coating (molecular weight: 3,500), which,

when it dissolved, propels a luminal unfolding microneedle injector (LUMI). The LUMI consists of three degradable arms, approximately 2.2 cm in length, that contain an array of 32, 1 mm long dissolving drug-loaded polymeric microneedles at each of their tips. The force exerted by the spring and the elastomeric nature of the LUMI ensures microneedle penetration into the surrounding tissue without the risk of perforation. After actuation, the LUMI is exposed to the intestinal fluid and begins to dissolve, with the non-degradable parts passing out of the GI tract without issue. The expansion of the device upon release from the tube and the pressing of the three arms against the intestinal wall does cause some distension. Further work is needed to ensure that this device does not cause discomfort to the patient due to intestinal distension that can be experienced unlike sharp sensations.

Other devices developed by the Langer group have utilised larger, millimetre-sized needles for the autonomous injection of biologics into the intestinal mucosa using a self-orientating device made from polymeric and metallic components [106]. This device, shown in Figure *3*E is called the self-orientating millimetre-scale applicator (SOMA) utilised a 7 mm long needle consisting of a 1.7 mm long, 1.2 mm diameter tip loaded with 0.3 mg of insulin on a stainless steel post. The endoscopically inserted device was characterised by injecting this needle into a porcine animal model's stomach mucosa. A compressed stainless steel spring with a spring constant *k* of between 0.1 to 0.5 N/mm and provided between 1.7 to 5 N of force when fully compressed was used to actuate the biodegradable needle into the tissue. Spring compression is maintained until the desired actuation point through the use of a sucrose cap that dissolves at a known rate when in contact with GI fluid passed to it through vents on the top side of the device. The timing of the sucrose cap dissolution, and hence the spring release, was tuned to the predicted time with a precision of 11.4 s within a 4 min period.

Microneedle based oral delivery of biologics has been commercialised by Rani Therapeutics (San Jose, CA, USA). This company has developed a hydroxypropyl methylcellulose capsule coated in an enteric coating composed of Eudragit L30-D55 and 0.1–0.5% Plasacryl-HTP20 that dissolves in the small intestine, releasing a polyethylene balloon-like device that inflates

due to carbon dioxide gas produced by a chemical reaction between citric acid and potassium bicarbonate. The inflated balloon orientates and injects a dissolvable drug-loaded microneedle into the intestinal lumen [96,97,107]. This device is shown in Figure *3*F-H and has successfully completed in human trials [97,108].

While the intestines are insensate to sharp sensations, they can detect distension and stretch. Tolerability studies with human volunteers of the RANI therapeutic capsule with balloons ranging in diameter from 21 mm to 25 mm demonstrated an absence of pain or discomfort when the balloons deployed, suggesting the forces generated were insufficient to activate intestinal stretch receptors. Safety studies of the capsule were only concerned with the excretion of the entire device, which was achieved. No histological examination of the tissue surrounding the needle injection site was reported in either study [96,97]. The capsule was reported to reliably deliver the drugs 80% of the time with the 25 mm diameter balloon after ingestion; reduced reliability was achieved with the smaller balloons. The bioavailability of octreotide delivered using this capsule was 65%, greater than the ≤ 1% obtained previously [109]. Pharmacokinetic data using the capsule is comparable to delivery via parenteral routes. However, the mass of drug that can be delivered with this technology is limited to 3.5 mg by the size of the needle. Additionally, the variability of GI transit times from person to person may preclude the use of this technology for time-sensitive therapeutics such as insulin, where predictability is crucial.

In addition to these capsules, other devices currently being developed that propose to use microneedles for oral drug delivery include the tissue attachment capsule developed at the University of Nebraska [110] and the magnetically actuated microneedle capsule from Daegu Gyeongbuk Institute of Science and Technology, Korea[111]. The tissue attachment capsule from the University of Nebraska is being commercialised by Progenity Inc [110]. This capsule incorporates a tissue attachment module (TAM), consisting of a radial array of microneedles inspired by the design of intestinal parasites that is intended for the attachment of a drug-carrying payload that separates from the capsule. Though *ex vivo* and *in vivo* studies have

been conducted to optimise the reliability of the TAM in attaching to the intestinal mucosa for an extended period [110][112], no studies have been published to date that demonstrate this technology for drug delivery.

The microneedle capsule shown in Figure *3*D was developed at Daegu Gyeongbuk Institute of Science and Technology, Korea, is unique from the other microneedle capsules. It incorporates a magnetic actuation system, which enables the capsule's location to be actively controlled by the clinician [111]. This capsule could carry three pyramidal, drug-loaded microneedle patches and use the magnetic system to sequentially release these patches at target lesions along the excised porcine intestinal tissue.

4.2.2. Epithelial Permeability

One means of improving the oral delivery of biologics through the intestinal epithelium is through reversible permeabilisation. This process involves applying some form of permeation enhancer that increases the transport of drugs through biological barriers, such as the intestinal epithelium. Commonly used permeation enhancers include various chemicals, electric fields and ultrasound [90].

Sonophoresis is the use of sound, more specifically, ultrasound, to enhance drug transport through biological barriers. The use of sonophoresis in intestinal drug delivery has been the subject of some recent research [113–115]. Low-frequency ultrasound (< 100 kHz) was demonstrated to be beneficial for increasing the uptake of drugs and potentially accelerating the treatment of GI disease [113]. Experiments conducted using *ex-vivo* porcine GI tissue measured the increased absorption of model therapeutics such as radiolabelled mesalamine and hydrocortisone that occurred when administered with ultrasound. The increase in absorption was dependent on the drug administered, the location along the GI tract, and the frequency of the ultrasound signal.

Further experiments involved inserting a proof of concept device into the rectum of anaesthetised porcine animal models. Initially, the ultrasound device was co-administered with

a mesalamine enema (4g in 60 ml suspension). A 20 kHz ultrasound signal of 7.5 Wcm^{-2} intensity was applied for 1 minute. Tissue biopsies that were taken immediately after the experiment showed that tissue uptake of the drug increased by a factor of 22. Further tests using insulin using the same experimental conditions used for the mesalamine showed a significant hypoglycemic response whereby ultrasound treated animals experienced a reduction in glucose levels of 83±9%, which was not observed in control animals not subjected to ultrasound. A blinded histological analysis detected no histological abnormalities in both the control and sonication groups [113].

Additional experiments to examine the suitability of this method for treating inflammatory bowel disease were conducted in a murine animal model with dextran sodium sulfate (DSS) induced colitis [113]. A mesalamine enema consisting of mesalamine (66.6 mg/ml) in a 0.5% w/w carboxymethyl cellulose (Sigma-Aldrich) solution in PBS was applied with and without a custom made 40 kHz radially emitting ultrasound rectal probe with a diameter of < 3 mm. Ultrasound was emitted for 0.5 seconds at 4.0 W. Ultrasound was administered every day or every other day or not at all with the enema. Colonic tissue histology was evaluated in a blinded fashion at the end of the 14-day trial. It was found that the tissue samples from mice subjected to ultrasound every day or every other day in conjunction with the mesalamine had less erosion of the epithelium and only minor shortening of the crypts when compared to other samples subjected to just the enema or no treatment. This murine experiment highlights the potential for this technology to treat GI disease, such as ulcerative colitis.

Miniaturised ultrasound transducers were integrated into a capsule format by Stewart et. al to assess the feasibility of *in vivo* ultrasound-mediated drug delivery trials in the porcine small bowel via smart pill [115]. An 11 mm diameter, 30 mm long tethered capsule, shown in Figure 3I and J, contained an integrated focused ultrasound transducer that emitted a 3.98 MHz signal and was inserted into the small bowel via a surgical stoma. This frequency was chosen based on earlier *in vitro* tests using Caco-2 monolayers [116,117]. The capsule delivered a solution consisting of fluorescent quantum dots and microbubbles into the small bowel through

the tether from an external syringe pump. When the ultrasound transducers were used to generate a signal with an acoustic intensity of 5.4±0.4 Wcm^{-2} for 90 seconds in conjunction with the delivery of the quantum dot, microbubble solution to the intestines, it was found that a fluorescent signal emanated from the intestinal tissue biopsies taken after the experiment. When insonation was not used with the quantum dot, microbubble solution, no fluorescence was observed. However, subsequent analysis of the tissue subjected to insonation and the quantum dot microbubble solution showed that the quantum dots were trapped in the intestinal mucus and did not manage to penetrate the epithelium. Further studies are required to demonstrate the feasibility of sonophoresis in a smart pill format.

Additionally, while a tethered capsule is useful for facilitating proof of concept studies to assess new means of imaging the GI tract, further work is needed to miniaturise the necessary systems to enable a fully integrated, wireless pill. The move towards wireless pills is advantageous for several reasons. For example, tethered devices are limited in their ability to access the entire length of the GI tract unless surgically inserted. Furthermore, tethered devices, whether inserted through naturally occurring orifices, can be uncomfortable for patients and require clinical staff for insertion. Though tethered devices provide a means of easy retrieval after use. Generally, smart pills are single-use devices, which is beneficial as it removes the risk of cross-contamination between patients, which is not unheard of with conventional endoscopes after sterilisation [118,119] and removes the additional design constraints imposed by repeated sterilisation [120]. The ability to retrieve such devices after use by the tether is only really of use in such proof of concept trials by enabling a focus on the development of the diagnostic or therapeutic modality, facilitating inspection of the integrity of the device or guiding or monitoring insertion via a surgical stoma [15].

4.3. Drug Adherence Monitoring

Nonadherence to a prescribed therapeutic regimen is highly prevalent, with 50% of patients not following prescribed treatments over time [121]. Poor medication adherence can significantly worsen the patients' health, lead to death, and increase healthcare costs [122–

124]. Despite the World Health Organisation (WHO) recognising the significant impact of greater medication adherence on public health compared to any improvement in a specific medical treatment [125], the ability to identify nonadherence by clinicians is limited [121]; its causes are complex [126] and attempts to improve adherence have either been mixed, complex or costly [127].

This challenging problem has spurred the development of several technological solutions [128,129], some of which take the form of an ingestible pill [130,131]. Two smart pills were commercialised and approved by regulatory authorities, the pill from Proteus Digital Health approved by the FDA in 2012 [132] and the Etect-Rx pill, also known as the ID-Cap pill, which the FDA approved in 2019. Proteus Digital Health subsequently closed in 2019, but their technology continues to be used in the Abilify MyCite system sold by Otsuka Pharmaceutical to monitor ingestion of aripiprazole [133].

The Proteus system consists of an ingestible device that emits an RF signal when it interacts with gastric acid, a wearable patch worn on the body to receive the signal and transmit it to the final part of the system, a phone which transmits the data from the pill to the clinician. The ingestible device consists of a 1 mm x 1 mm x 0.3 mm silicon integrated circuit that has been coated with an 8 μm thin film of magnesium on the underside of the chip, while a 9 μm thick gold film is deposited followed by 7 μm of cuprous chloride on the top surface of the chip, where the functional elements of the integrated circuit reside. This modified integrated circuit is attached to a 0.3 mm thick and 0.5 mm diameter disc of insulating material composed of ethyl cellulose, hydroxypropyl cellulose and triethyl citrate. When in contact with gastric acid, the magnesium and cuprous chloride films act together to form a battery. The charge created by that electrochemical reaction is collected by the gold film and used to power the device to transmit a signal to the external patch until the electrode materials are exhausted by the chemical reaction [130]. The Etect-Rx system is similar in some respects to the Proteus system, though one significant difference is the use of an electronic lanyard to collect signal data from the pill rather than the wearable electronic patch used in the Proteus system. The

Etect-Rx ingestible device is embedded in the oral dosage form. It consists of a flexible printed circuit board containing an antenna; epoxy coated integrated circuits, two electrodes one made from magnesium chloride and the other silver chloride, all connected with metallic silver interconnects [131]. Such systems were found to be generally safe [134,135], stable over extended periods [136] and did not affect the quality of the formulation [137,138].

Several studies have been conducted to assess the efficacy of such devices in improving adherence [139–141]. One study investigating the use of the Proteus digital health system on patients with hypertension showed significantly improved clinical outcomes in participants using the system over 4 and 12 weeks compared to those who did not use it. However, the Proteus pill trial participants were also given lifestyle coaching and education opportunities, unlike those who were not given the Proteus pill. Furthermore, adherence to treatment by the participants not taking the Proteus pill was not measured. Due to these factors, the improvements in health observed during the clinical trial in participants that took the Proteus pill should not be attributed solely to the Proteus system [141]. A randomised controlled trial to evaluate adherence during tuberculosis treatment in a sample population divided between those using the Proteus system and those being treated using directly observed therapies (DOTs) found increased adherence in the sample treated using Proteus (92.9%) compared to DOTs (63.1%) [140]. However, statistical analysis showed that the difference observed could be mainly attributed to the fact that the Proteus system could monitor adherence 7 days a week, whereas DOTs could only do so on working days. When this was factored in to enable a like for like comparison, the adherence for Proteus dropped to 95.6% compared to 92.6% for DOTs [140]. Another study investigating whether adherence was improved in those being treated for Hepatitis C were single-arm clinical trials, limiting the strength of any findings [139]. Critical analyses have also cast doubt on the efficacy of the technology in improving adherence in populations with serious mental health issues treated with aripiprazole [142,143].

Whether this technology is effective at improving adherence is inconclusive, and further study is needed. However, accurate and reliable measurement of adherence is an issue with many

clinical studies, and this technology may provide a more confident measurement of adherence than other technological solutions, such as medication event monitoring systems that measure when a pill bottle or blister pack has been opened [137,144,145]. This is because it is more challenging to hide nonadherence with these ingestible devices as the electrical signal is generated only when the pill interacts with gastric acid. This is evidenced by the fact that these digital pills detected ingestion with accuracies greater than 84% [143].

4.4. Non-Pharmacological Therapeutic Smart Pills

As shown, various smart pills have been developed for the delivery of pharmaceuticals for therapeutic purposes. However, effective pharmaceutical therapies may not exist for all conditions requiring the use of non-pharmacological approaches. Examples of non-pharmacological approaches include electrical stimulation and intragastric balloons, amongst others. Recognition of the importance of non-pharmacological approaches has spurred their miniaturisation and integration into a smart pill format for treating obesity, constipation and dysmotility.

4.4.1. Obesity

Due to the significant health burden associated with the obesity epidemic, a number of ingestible smart pills have been created for the treatment of obesity [146–152]. These devices work on similar principles to intragastric balloons (IGB), in which a balloon is inflated using air or saline to a volume ranging from 250 to 950 ml and resides in the stomach for 1 to 12 months, depending on clinical recommendations [153]. The resident balloon takes up space in the stomach, causing the patient to feel satiated quicker after ingesting food leading to loss of appetite and weight loss [154,155]. The development of ingestible capsules for treating obesity was predominantly spurred by the need for endoscopic procedures and patient sedation to place and remove the IGB, which can be costly and result in patient discomfort, vomiting, mucus damage and nausea [156]. The integration of an IGB into an easily swallowed pill

removes these disadvantages while also providing a means of post-implantation adjustment of the balloon volume.

The same group has mostly done the development of ingestible IGB pills at Nanyang Technological University, Singapore [146,148–152] though other capsules have been developed elsewhere [147]. The Singaporean group's earliest prototype utilised a chemical reaction between gastric acid and bicarbonates stored within the deflated balloon to generate the gas needed to inflate the balloon. Ingress of the surrounding acid into the balloon was controlled using a plunger actuator controlled in real-time via wireless communications between the lithium-ion battery-powered electronic capsule and an external controller. The remote control of the actuator also triggered deflation of the balloon and control of balloon volume by control of the chemical reaction. This prototype was 57 mm in diameter and 157 mm in length due to the onboard components' size, significantly larger than could be ingested. This prototype's balloon was successfully inflated to a volume of 200 ml when surgically implanted in a pigs stomach.

Subsequent capsules removed the need for onboard actuation mechanisms through the use of integrated magnets coupled to an external magnetic field, reducing the capsule size to a diameter of 9.6 mm and length of 27 mm [148]. In this capsule, the south pole of the external magnet is brought close to the patient, opening the valve between 60% citric acid and potassium bicarbonate chambers within the ingested capsule, resulting in carbon dioxide production that was measured to inflate the balloon to a volume of 154.18 ± 5.72 ml. Alignment of the capsule with the north pole of the external magnet is also used to trigger deflation, after which the capsule is excreted. This device was subsequently refined and tested *in vivo* by the endoscopic placement of the device with a female adult porcine stomach and a female human adult volunteer [150,152]. The balloon was demonstrated to inflate to 120 ml within 6 minutes and left to reside for a week within the porcine stomach with no adverse effects or signs of discomfort observed. The trial with the human female adult volunteer was designed to assess the time taken for inflation to begin and the duration before the balloon was fully inflated. The

capsule took 1 minute to inflate the balloon fully to 120 ml and was immediately pierced afterwards. The number of *in vivo* trials conducted to date is insufficient to determine the efficacy of this technology. Furthermore, the fully inflated balloons' volume is less than that of clinically used IGBs though it is expected that this could be solved by ingesting multiple IGB capsules.

4.4.2. Constipation

Constipation is a common disorder that is, in most cases, related to some dysfunction of the GI tract. There is a need for innovative solutions to this condition due to the high-cost burden on healthcare systems linked to chronic constipation [157], the high prevalence of the condition [158], poor quality of life [159] and low patient satisfaction with current treatments [160]. One proposed solution is the VIBRANT capsule (Vibrant Ltd. Yokneam, Israel), which is a 24 x 11 mm vibrating ingestible capsule [161–163]. This battery-powered capsule consists of two segments that are attached together but free to move independently. The actuation of the two segments is achieved by an internal ferromagnetic shaft connected to a solenoid and springs. External control of the current flowing through the solenoid enables the frequency, magnitude and duration of vibrations within the colon to be adjusted. Initial *in vivo* trials with 26 human adult patients reported an increase of spontaneous bowel movements (SBMs) in 23 patients, with the mean number of SBMs/week increasing from 2.19±0.67 to 3.79±1.31. However, 12 members of the study reported adverse effects potentially related to the study, such as abdominal pain, diarrhoea, flatulence and gastroenteritis [161]. However, subsequent *in vivo* human studies showed no significant difference in the number of SBMs between those given the VIBRANT capsule and those given a sham capsule [162,163] though no significant adverse effects were reported that were related to the VIBRANT capsule. Further optimisation of the vibration parameters of the capsule have been repeatedly proposed as a means of increasing device efficacy.

4.4.3. Electrical Stimulation

Multiple studies have demonstrated that electrical stimulation can modulate GI motility and, therefore, may be a promising alternative to pharmacological treatments of GI dysmotility [164]. Implantable electrical stimulation devices for treating gastroparesis [165] and obesity [166] are in clinical use. A proof of concept, ingestible device was recently demonstrated to induce muscle contraction within the stomach through electrical stimulation [167]. The device was based on an earlier self-orientating capsule design [106], with the stainless steel needle of that device connected to an external microcontroller and silver oxide battery via flexible stranded core wires. These external electrical components were encapsulated in a layer of PDMS to protect them from the gastric acid, and a thin layer of Parylene C was deposited onto the shaft of the needle to target electrical current flow into the lower muscular layer of the stomach tissue via the uncoated, conductive needle tips. The self-orientating nature and the effect of gravity led the device to settle in the stomach location near to where gastric pacemakers are typically placed. The microcontroller was used to mimic the pulses created by a FDA-authorised gastric electrical stimulation system by generating two consecutive voltage pulses of length 330 μs with a 70 ms gap in between. These pulses were repeated every 5 seconds. The voltage pulse amplitude within the stomach was measured to range between 0.31 to 0.42 V, and was intended to generate a charge density at the electrode-tissue interface of 2.2 $\mu C.cm^{-2}$. Three devices were tested in adult porcine animal models and muscular stimulation was observed via ultrasound imaging. As recognised by the authors, future devices should use needles made from platinum or iridium to avoid corrosion and use a current-controlled system to mitigate the effects of changing electrical impedance on stimulation due to tissue fibrosis. The device only remains attached to the stomach in the absence of digestion, limiting the use of this technology to applications where short term or repeated interventions are required. This will also require further studies to assess this technology's efficacy in humans with gastroparesis.

5. Future Directions for Therapeutic Smart Pills

Whether the smart pill is being used to deliver a pharmacological or non-pharmacological treatment, there are some commonalities in the technical challenges that must be overcome to expedite translation, such as anchoring and localisation.

Anchoring is the ability of the smart pill to remain fixed in position along the GI tract while administering the treatment. The anchoring method should be able to withstand peristaltic and other forces acting on objects within the GI tract. The ability to anchor the pill in place would benefit the reliability of therapeutic smart pills by minimising the variation in transit time between individuals and along the GI tract. Additionally, anchoring would allow the delivery of specific amounts of the pharmaceutical or duration of non-pharmacological treatments at the target location, improving the effectiveness of the therapies. Various methods have been proposed to anchor pills in the GI tract, ranging from microneedles [168], needles [169], magnets [170,171] and biomimetic adhesives [172,173]. Further testing with greater sample populations is required to fully assess the efficacy of these solutions under conditions where the anchor mechanisms would be exposed to peristalsis, boluses, and other forces due to the greater reliability needed if they are to be used to ensure the targeted delivery of therapeutics.

For anchoring to be feasible, the challenge of localisation must also be addressed. Localisation is the ability of the smart pill to identify its position and orientation with reference to some external or internal frame of reference. An internal frame of reference can include anatomical landmarks or sites of pathology; external frames of reference, such as telemetry antenna, are commonly used. The use of internal frames of reference will require the integration of sensing and imaging modalities to recognise these landmarks, impacting the internal volume of the pill available for therapeutic delivery. Accurate information on pill position and orientation is necessary to ensure therapeutic delivery at the desired location. Current methods of localisation used in capsule endoscopy rely on triangulation via eight antennae worn in a belt around the abdomen, resulting in an average error of 37.7 mm [6], which is lower than what would be required for therapeutic delivery. The GI tract's deformable

nature further complicates the ability to locate the pill in real-time accurately and may require both external and internal frames of reference.

Another challenge, specific to smart pills that deliver pharmacological therapeutics, is the onboard storage volume. Most smart pills developed to date have storage volumes between 0.3 to 1 ml due to onboard electronics, telemetry, batteries, actuators, sensors, and other components that take up space. As these devices become more sophisticated due to increased electronic and mechanical integration, there will be implications for dosages achievable with these pills. This factor may necessitate greater pharmaceutical potency or increased reliance on miniaturisation technology such as microelectromechanical systems or microfluidics to reduce the size of mechanical components. Integration of these systems within the pill also has economic implications for this technology due to the associated increase in cost. This may make it prohibitive to use this technology to treat many conditions until advantages of scale enable greater usage. Another factor to consider is the sustainability of this technology due to the nature of these pills being single-use and their removal of the body via excretion. If the technology comes into wider use, then there may be environmental challenges to consider due to increased electronic waste. This may be avoided by a shift towards biodegradable materials, though the use of such materials in creating electronic components is still in its infancy [174].

6. Smart Pills for Biopsy and Sampling.

Since their advent, smart pills have been proposed for a variety of clinical applications. One application that has received much interest is pills that can be used to conduct tissue biopsies or to sample the GI environment due to the promised benefits of reduced invasiveness and little or no patient recovery time. The surgical acquisition of tissue via endoscopic biopsy necessitates several processes to be conducted before surgery, such as fasting and bowel preparation through the ingestion of laxatives to ensure a clear, unobstructed bowel for imaging to locate the biopsy site and to mitigate the risk of a contaminated sample. The patient may also be sedated immediately before endoscopic insertion. The endoscopic working

channel is used to deploy surgical instruments to acquire tissue samples or suction to collect aspirated intestinal fluid. However, due to the transit of the endoscope through the GI tract, the working channel can be easily contaminated by oral and GI contents. This can have a significant impact on the accuracy of microbiome samples collected via endoscopic aspiration. Ingestible sampling or biopsy devices have the potential to overcome several of these disadvantages associated with conventional clinical methods.

The sample volume obtainable with these smart pills is determined by the size of the capsule, which is comparable to the dimensions of other smart pills to mitigate the risk of retention, as well as the internal volume taken up by other integrated electronic or mechanical systems and the minimum volume required by the analysis to be performed after capsule collection.

6.1. Tissue Biopsy

The Crosby capsule, developed in 1957, is an 11 mm in diameter and 20 mm in length stainless steel capsule connected to a polyethylene tube designed for jejunal biopsies [175]. An external syringe is used to create a negative pressure that draws mucosal tissue through a 5 mm aperture in the side of the capsule, triggers the rotation of an integrated knife that biopsies the mucosal tissue. Though the Crosby capsule provides high diagnostic value biopsies for several conditions, the design was associated with complications such as bleeding and perforation [176–178]. Furthermore, withdrawal of the device from the patient occasionally necessitated the administration of propantheline bromide, an antimuscarinic agent, to relax spasms of the pylorus [179].

Since the introduction of the Crosby capsule, several other capsules for the biopsy of tissue have been proposed [180–185]. Some of these are similar to the Crosby capsule [186], while other, more recent designs aim for wireless capsule biopsy. These wireless capsules have been predominantly tested under *in vitro* and *ex vivo* conditions. These results leave unanswered how well biopsies taken with such capsules remain uncontaminated by other sources under clinical conditions and whether there are risks of bleeding and perforation from

such capsules. Furthermore, the limited biopsy storage volume available within these capsules would require the ingestion of multiple capsules for multiple biopsies.

6.2. Microbiome Sampling

The link between the GI microbiome and health is widely recognised, with cumulative evidence of the relationship between changes in the GI microbiome to GI disease [187]. Due to the ease of collection, non-invasiveness and ease at repeated sampling, faecal samples are commonly used as proxies for GI microbiome studies. However, several studies have highlighted the limitations of this method due to the differences in the faecal microbiome compared to that of the GI microbiome [188–192]. Other methods of sampling the GI microbiome, such as aspiration and mucosal biopsy, are at risk of sample contamination [193–196] or inducing temporary changes in the microbiome such its composition and diversity so the sample may not be an accurate reflection of the microbiome [197,198].

Several pills, some of which are shown in Figure *4*, have been demonstrated that sample the GI microbiome [199–202]. These capsules use various sampling methods such as springs and wicking materials [199], shape memory alloys [200], osmotic pumps [201], biodegradable coatings [202]. Most of these pills sampled along the entire length of the GI tract and have not demonstrated sampling within specific regions of the GI tract. Information on whether they can be used to determine the spatial distribution of the microbiome along the GI tract, which would be advantageous over widely used faecal proxies, does not exist. One pill, shown in Figure *4*B, was designed to sample the microbiome within the mucus layer and reseal after capture, though *in vivo* tests have yet to be conducted [200]. The rest of the pills reported to date, such as those in Figure *4*A and C, sample the microbiota of the luminal fluid and not that of the mucus. Where sampling occurs and what is sampled has implications for the quality of the information derived from such devices. This is because the composition and diversity of the microbiome varies longitudinally along the GI tract and axially, from the lumen to the mucosal surface [203,204].

7. Future Directions of Smart Pills

This review shows that, despite the clinical potential of these devices, smart pills are still in their infancy. Despite the flurry of research activity in smart pills, many are yet to undergo the extensive *in vivo* testing necessary to demonstrate these technologies' diagnostic or therapeutic efficacy. The vision of autonomous smart pills capable of diagnosis with minimal clinical involvement and simultaneously applying treatment is some way off. The increased complexity of such devices may make these devices prohibitive in cost, thereby denying wider patient benefit and make the devices more at risk of failure. It is more probable that instead of one pill capable of all functions, a family of pills will be created, their designs each optimised to perform a specific function, and work together or in sequence to ensure patient well-being. This strategy is similar to the increasing specialisation of CEs, with the capsules modified for optimal performance in different parts of the GI tract by adding additional cameras or utilising different frame rates. Either way, for this technology to mature and live to its full clinical potential, several technical challenges must be overcome. These challenges include but are not limited to localisation, navigation and greater intelligence. The solutions to these challenges will be intrinsically interdisciplinary, requiring expertise from electronic engineering, mechanical engineering, computer science, microengineering and materials science. Increasing smart pill functionality to incorporate navigation, multiple diagnostic or therapeutic modalities, and localisation, coupled with design constraints to ensure ease of ingestion and safety [205], will bring new challenges. For example, greater systems integration brings the risk of power consumption will be especially challenging since batteries currently take up a large amount of space in capsule endoscopes. This will require new solutions to ensure that space is available for other functions. This is especially pressing for developing therapeutic smart pills, especially drug delivery smart pills, where space is vital for the pharmaceutical payload.

8. References

[1] W.H. Steinberg, F.A. Mina, P.G. Pick, G.H. Frey, Heidelberg Capsule I, J. Pharm. Sci.

54 (1965) 772–776. https://doi.org/10.1002/jps.2600540522.

[2] S.P. Eriksen, J. V. Swintosky, E.J. Serfass, T.H. Lin, J. Abrams, F.M. Sturtevant, Equipment and methodology for relating gastrointestinal absorption to site of drug release, J. Pharm. Sci. 50 (1961) 151–156. https://doi.org/10.1002/jps.2600500213.

[3] I. Wilding, P. Hirst, A. Connor, Wilding, Hirst, Connor, Development of a new engineering-based capsule for human drug absorption studies, Pharm. Sci. Technolo. Today. 3 (2000) 385–392. https://doi.org/10.1016/S1461-5347(00)00311-4.

[4] G. Iddan, G. Meron, A. Glukhovsky, P. Swain, Wireless capsule endoscopy, Nature. 405 (2000) 417–418. http://adsabs.harvard.edu/abs/2000Natur.405..417I (accessed September 9, 2013).

[5] G.J. Iddan, C.P. Swain, History and development of capsule endoscopy, Gastrointest. Endosc. Clin. N. Am. 14 (2004) 1–9. https://doi.org/10.1016/j.giec.2003.10.022.

[6] G. Cummins, B.F. Cox, G. Ciuti, T. Anbarasan, M.P.Y. Desmulliez, S. Cochran, R. Steele, J.N. Plevris, A. Koulaouzidis, Gastrointestinal diagnosis using non-white light imaging capsule endoscopy, Nat. Rev. Gastroenterol. Hepatol. 16 (2019) 429–447. https://doi.org/10.1038/s41575-019-0140-z.

[7] R.A. Enns, L. Hookey, D. Armstrong, C.N. Bernstein, S.J. Heitman, C. Teshima, G.I. Leontiadis, F. Tse, D. Sadowski, Clinical Practice Guidelines for the Use of Video Capsule Endoscopy, Gastroenterology. 152 (2017) 497–514. https://doi.org/10.1053/j.gastro.2016.12.032.

[8] D. Hartmann, A. Eickhoff, U. Damian, J.F. Riemann, Diagnosis of small-bowel pathology using paired capsule endoscopy with two different devices: a randomized study., Endoscopy. 39 (2007) 1041–5. https://doi.org/10.1055/s-2007-966943.

[9] S.P. Hong, J.H. Cheon, T. Il Kim, S.Y. Song, W.H. Kim, Comparison of the diagnostic yield of “MiroCam” and “PillCam SB” capsule endoscopy., Hepatogastroenterology. 59

(2012) 778–81. https://doi.org/10.5754/hge10472.

[10] M. Rahman, S. Akerman, B. DeVito, L. Miller, M. Akerman, K. Sultan, Comparison of the diagnostic yield and outcomes between standard 8 h capsule endoscopy and the new 12 h capsule endoscopy for investigating small bowel pathology., World J. Gastroenterol. 21 (2015) 5542–7. https://doi.org/10.3748/wjg.v21.i18.5542.

[11] H. Niwa, H. Tajiri, M. Nakajima, K. Yasuda, eds., New Challenges in Gastrointestinal Endoscopy, Springer Japan, Tokyo, 2008. https://doi.org/10.1007/978-4-431-78889-8.

[12] B.C. Dickson, C.J. Streutker, R. Chetty, Coeliac disease: an update for pathologists., J. Clin. Pathol. 59 (2006) 1008–16. https://doi.org/10.1136/jcp.2005.035345.

[13] M.A. Al-Rawhani, J. Beeley, D.R.S. Cumming, Wireless fluorescence capsule for endoscopy using single photon-based detection, Sci. Rep. 5 (2015) 18591. https://doi.org/10.1038/srep18591.

[14] J.H. Lee, G. Traverso, C.M. Schoellhammer, D. Blankschtein, R. Langer, K.E. Thomenius, D.S. Boning, B.W. Anthony, Towards wireless capsule endoscopic ultrasound (WCEU), in: 2014 IEEE Int. Ultrason. Symp., IEEE, 2014: pp. 734–737. https://doi.org/10.1109/ULTSYM.2014.0181.

[15] H.S. Lay, M.P.Y. Desmulliez, S. Cochran, G. Cummins, B.F. Cox, Y. Qiu, M.V. Turcanu, R. McPhillips, C. Connor, R. Gregson, E. Clutton, In-Vivo Evaluation of Microultrasound and Thermometric Capsule Endoscopes, IEEE Trans. Biomed. Eng. 66 (2019) 632–639. https://doi.org/10.1109/TBME.2018.2852715.

[16] N. Gluck, B. Shpak, R. Brun, T. Rösch, N. Arber, M. Moshkowitz, A novel prepless X-ray imaging capsule for colon cancer screening, Gut. 65 (2016) 371–373. https://doi.org/10.1136/gutjnl-2015-310893.

[17] M.J. Gora, J.S. Sauk, R.W. Carruth, K.A. Gallagher, M.J. Suter, N.S. Nishioka, L.E. Kava, M. Rosenberg, B.E. Bouma, G.J. Tearney, Tethered capsule endomicroscopy

enables less invasive imaging of gastrointestinal tract microstructure, Nat. Med. 19 (2013) 238–240. https://doi.org/10.1038/nm.3052.

[18] K. Liang, G. Traverso, H.-C. Lee, O.O. Ahsen, Z. Wang, B. Potsaid, M. Giacomelli, V. Jayaraman, R. Barman, A. Cable, H. Mashimo, R. Langer, J.G. Fujimoto, Ultrahigh speed en face OCT capsule for endoscopic imaging, Biomed. Opt. Express. 6 (2015) 1146. https://doi.org/10.1364/BOE.6.001146.

[19] Z. Huang, W. Zheng, S. Xie, R. Chen, H. Zeng, D.I. McLean, H. Lui, Laser-induced autofluorescence microscopy of normal and tumor human colonic tissue, Int. J. Oncol. 24 (2004) 59–63. https://doi.org/10.3892/ijo.24.1.59.

[20] J. Wang, F. Memon, G. Touma, S. Baltsavias, J.H. Jang, C. Chang, M.F. Rasmussen, E. Olcott, R.B. Jeffrey, A. Arbabian, B.T. Khuri-Yakub, Capsule ultrasound device: Characterization and testing results, in: 2017 IEEE Int. Ultrason. Symp., IEEE, 2017: pp. 1–4. https://doi.org/10.1109/ULTSYM.2017.8092071.

[21] Y. Qiu, Y. Huang, Z. Zhang, B.F. Cox, R. Liu, J. Hong, P. Mu, H.S. Lay, G. Cummins, M.P.Y. Desmulliez, E. Clutton, H. Zheng, W. Qiu, S. Cochran, Ultrasound Capsule Endoscopy With a Mechanically Scanning Micro-ultrasound: A Porcine Study, Ultrasound Med. Biol. 46 (2020) 796–804. https://doi.org/10.1016/j.ultrasmedbio.2019.12.003.

[22] J.C. Norton, P.R. Slawinski, H.S. Lay, J.W. Martin, B.F. Cox, G. Cummins, M.P.Y. Desmulliez, R.E. Clutton, K.L. Obstein, S. Cochran, P. Valdastri, Intelligent magnetic manipulation for gastrointestinal ultrasound, Sci. Robot. 4 (2019) eaav7725. https://doi.org/10.1126/scirobotics.aav7725.

[23] J.H. Lee, G. Traverso, D. Ibarra-zarate, B.W. Anthony, Ex Vivo and In Vivo Imaging Study of Ultrasound Capsule Endoscopy, J. Med. Device. 14 (2020). https://doi.org/10.1115/1.4046352.

[24] R. Gregson, S. Greenhalgh, B. Cox, S. Cochrane, R.E. Clutton, Feeding management before gastrointestinal studies in pigs:, Https://Doi.Org/10.1177/0023677220960509. 55 (2020) 177–180. https://doi.org/10.1177/0023677220960509.

[25] A. Shiotani, A.R. Opekun, D.Y. Graham, Visualization of the Small Intestine Using Capsule Endoscopy in Healthy Subjects, Dig. Dis. Sci. 52 (2007) 1019–1025. https://doi.org/10.1007/s10620-006-9558-6.

[26] Y. Kimchy, R. Lifshitz, S. Lewkowitz, G. Bertuccio, N. Arber, N. Gluck, P.J. Pickhardt, Radiographic capsule-based system for non-cathartic colorectal cancer screening, Abdom. Radiol. 42 (2017) 1291–1297. https://doi.org/10.1007/s00261-016-1026-y.

[27] US Food and Drug Administration, What are the Radiation Risks from CT ?, FDA Website. (n.d.). https://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/MedicalX-Rays/ucm115329.htm (accessed April 26, 2018).

[28] R.E. van Gelder, H.W. Venema, I.W.O. Serlie, C.Y. Nio, R.M. Determann, C.A. Tipker, F.M. Vos, A.S. Glas, J.F.W. Bartelsman, P.M.M. Bossuyt, J.S. Laméris, J. Stoker, CT Colonography at Different Radiation Dose Levels: Feasibility of Dose Reduction, Radiology. 224 (2002) 25–33. https://doi.org/10.1148/radiol.2241011126.

[29] T.-H. Tsai, J. Fujimoto, H. Mashimo, Endoscopic Optical Coherence Tomography for Clinical Gastroenterology, Diagnostics. 4 (2014) 57–93. https://doi.org/10.3390/diagnostics4020057.

[30] B. Shen, G. Zuccaro, T.L. Gramlich, N. Gladkova, P. Trolli, M. Kareta, C.P. Delaney, J.T. Connor, B.A. Lashner, C.L. Bevins, F. Feldchtein, F.H. Remzi, M.L. Bambrick, V.W. Fazio, In vivo colonoscopic optical coherence tomography for transmural inflammation in inflammatory bowel disease., Clin. Gastroenterol. Hepatol. 2 (2004) 1080–7. http://www.ncbi.nlm.nih.gov/pubmed/15625653.

[31] S.L.S. Halder, G.R. Locke, C.D. Schleck, A.R. Zinsmeister, L.J. Melton, N.J. Talley, Natural History of Functional Gastrointestinal Disorders: A 12-year Longitudinal Population-Based Study, Gastroenterology. 133 (2007) 799-807.e1. https://doi.org/10.1053/j.gastro.2007.06.010.

[32] N.J. Talley, Functional gastrointestinal disorders as a public health problem, Neurogastroenterol. Motil. 20 (2008) 121–129. https://doi.org/10.1111/j.1365-2982.2008.01097.x.

[33] R.J. Saad, W.L. Hasler, A technical review and clinical assessment of the wireless motility capsule., Gastroenterol. Hepatol. (N. Y). 7 (2011) 795–804. http://www.ncbi.nlm.nih.gov/pubmed/22347818.

[34] P. Li, C. Kreikemeier-Bower, W. Xie, V. Kothari, B.S. Terry, Design of a Wireless Medical Capsule for Measuring the Contact Pressure Between a Capsule and the Small Intestine, J. Biomech. Eng. 139 (2017) 051003. https://doi.org/10.1115/1.4036260.

[35] A. Benken, Y. Gianchandani, Passive Wireless Pressure Sensing for Gastric Manometry, Micromachines. 10 (2019) 868. https://doi.org/10.3390/mi10120868.

[36] C.-H. Liao, C.-T. Cheng, C.-C. Chen, U.-M. Jow, C.-H. Chen, Y.-L. Lai, Y.-C. Chen, D.-R. Ho, An Ingestible Electronics for Continuous and Real-Time Intraabdominal Pressure Monitoring, J. Pers. Med. 11 (2020) 12. https://doi.org/10.3390/jpm11010012.

[37] D.J. Casa, L.E. Armstrong, M.S. Ganio, S.W. Yeargin, Exertional Heat Stroke in Competitive Athletes, Curr. Sports Med. Rep. 4 (2005) 309–317. https://doi.org/10.1097/01.CSMR.0000306292.64954.da.

[38] HQ inc, CorTemp Capsule, HQ Inc Website. (n.d.). https://hqinc.net/home/cortemp/cortemp-products/cortemp-sensor/ (accessed February 4, 2021).

[39] Equi-vital, VitalSense Core Temperature Capsule, Equi-Vital Website. (n.d.).

https://www.equivital.com/core-temperature (accessed February 4, 2021).

[40] BodyCAP, E-Celsius, BodyCAP Website. (n.d.). https://www.bodycap-medical.com/e-celsius-performance-body-temperature-monitoring-telemetric-pill/ (accessed February 4, 2021).

[41] MyTemp BV, MyTemp, MyTemp Website. (n.d.). http://mytemp.eu/ (accessed February 4, 2021).

[42] P. Mojaverian, Evaluation of gastrointestinal pH and gastric residence time via the Heidelberg radiotelemetry capsule: Pharmaceutical application, Drug Dev. Res. 38 (1996) 73–85. https://doi.org/10.1002/(SICI)1098-2299(199606)38:2<73::AID-DDR1>3.0.CO;2-H.

[43] A.D. Farmer, S.M. Scott, A.R. Hobson, Gastrointestinal motility revisited: The wireless motility capsule., United Eur. Gastroenterol. J. 1 (2013) 413–21. https://doi.org/10.1177/2050640613510161.

[44] L. Lu, G. Yan, K. Zhao, F. Xu, An implantable telemetry platform system with ASIC for in vivo monitoring of gastrointestinal physiological information, IEEE Sens. J. 15 (2015) 3524–3534. https://doi.org/10.1109/JSEN.2015.2392105.

[45] M.A. Kwiatek, J.E. Pandolfino, The Bravo™ pH capsule system, Dig. Liver Dis. 40 (2008) 156–160. https://doi.org/10.1016/j.dld.2007.10.025.

[46] P.J. van der Schaar, J.F. Dijksman, H. Broekhuizen-de Gast, J. Shimizu, N. van Lelyveld, H. Zou, V. Iordanov, C. Wanke, P.D. Siersema, A novel ingestible electronic drug delivery and monitoring device, Gastrointest. Endosc. 78 (2013) 520–528. https://doi.org/10.1016/j.gie.2013.03.170.

[47] G. Cummins, D.E. Yung, B.F. Cox, A. Koulaouzidis, M.P.Y. Desmulliez, S. Cochran, Luminally expressed gastrointestinal biomarkers, Expert Rev. Gastroenterol. Hepatol. 11 (2017) 1119–1134. https://doi.org/10.1080/17474124.2017.1373017.

[48] A. Nemiroski, M. Ryou, C.C. Thompson, R.M. Westervelt, Swallowable fluorometric capsule for wireless triage of gastrointestinal bleeding, Lab Chip. 15 (2015) 4479–4487. https://doi.org/10.1039/C5LC00770D.

[49] P. Qiao, H. Liu, X. Yan, Z. Jia, X. Pi, A Smart Capsule System for Automated Detection of Intestinal Bleeding Using HSL Color Recognition, PLoS One. 11 (2016) e0166488. https://doi.org/10.1371/journal.pone.0166488.

[50] S. Schostek, M. Zimmermann, J. Keller, M. Fode, M. Melbert, M.O. Schurr, T. Gottwald, R.L. Prosst, Telemetric real-time sensor for the detection of acute upper gastrointestinal bleeding, Biosens. Bioelectron. 78 (2016) 524–529. https://doi.org/10.1016/j.bios.2015.11.073.

[51] M. Ryou, A. Nemiroski, D. Azagury, S.N. Shaikh, M.B. Ryan, R.M. Westervelt, C.C. Thompson, An implantable wireless biosensor for the immediate detection of upper GI bleeding: A new fluorescein-based tool for diagnosis and surveillance (with video), Gastrointest. Endosc. 74 (2011) 189-194.e1. https://doi.org/10.1016/j.gie.2011.03.1182.

[52] M. Zimmermann, T. Gottwald, M.O. Schurr, S. Schostek, Assessing a novel diagnostic medical device: Pragmatic route from lab to clinic, Int. Symp. Med. Inf. Commun. Technol. ISMICT. 2019-May (2019) 2019–2022. https://doi.org/10.1109/ISMICT.2019.8743888.

[53] S. Schostek, M. Zimmermann, J. Keller, M. Fode, M. Melbert, M.O. Schurr, T. Gottwald, R.L. Prosst, Volunteer Case Series of a New Telemetric Sensor for Blood Detection in the Upper Gastrointestinal Tract: The HemoPill, Dig. Dis. Sci. 61 (2016) 2956–2962. https://doi.org/10.1007/s10620-016-4226-y.

[54] M. Mimee, P. Nadeau, A. Hayward, S. Carim, S. Flanagan, L. Jerger, J. Collins, S. McDonnell, R. Swartwout, R.J. Citorik, V. Bulović, R. Langer, G. Traverso, A.P. Chandrakasan, T.K. Lu, An ingestible bacterial-electronic system to monitor

gastrointestinal health, Science (80-.). 360 (2018) 915–918. https://doi.org/10.1126/science.aas9315.

[55] K. Twomey, E. Alvarez de Eulate, J.R. Marchesi, S. Kolida, G. Gibson, D.W.M. Arrigan, V.I. Ogurtsov, Characterization of the Electrochemical Behavior of Gastrointestinal Fluids Using a Multielectrode Sensor Probe, IEEE Trans. Biomed. Eng. 58 (2011) 2521–2527. https://doi.org/10.1109/TBME.2011.2158543.

[56] K. Kalantar-zadeh, C.K. Yao, K.J. Berean, N. Ha, J.Z. Ou, S.A. Ward, N. Pillai, J. Hill, J.J. Cottrell, F.R. Dunshea, C. McSweeney, J.G. Muir, P.R. Gibson, Intestinal Gas Capsules: A Proof-of-Concept Demonstration, Gastroenterology. 150 (2016) 37–39. https://doi.org/10.1053/j.gastro.2015.07.072.

[57] K. Kalantar-Zadeh, K.J. Berean, N. Ha, A.F. Chrimes, K. Xu, D. Grando, J.Z. Ou, N. Pillai, J.L. Campbell, R. Brkljača, K.M. Taylor, R.E. Burgell, C.K. Yao, S.A. Ward, C.S. McSweeney, J.G. Muir, P.R. Gibson, A human pilot trial of ingestible electronic capsules capable of sensing different gases in the gut, Nat. Electron. 1 (2018) 79–87. https://doi.org/10.1038/s41928-017-0004-x.

[58] Atmo Biosciences, Atmo Biosciences, (n.d.). https://atmobiosciences.com/ (accessed March 31, 2021).

[59] Atmo Biosciences, Atmo Biosciences' ingestible gas-sensing capsule to be used in Swedish IBS trial led by Professor Magnus Simrén, (n.d.). https://atmobiosciences.com/atmo-biosciences-ingestible-gas-sensing-capsule-to-be-used-in-swedish-ibs-trial/ (accessed March 31, 2021).

[60] S. Singh, N. Allan, C. Wahl, S.N. Lee, E. Chuang, M.L. Jones, Sa1717 – Development of a Swallowable Diganostic Capsule to Monitor Gastrointestinal Health, Gastroenterology. 156 (2019) S-376. https://doi.org/10.1016/S0016-5085(19)37784-4.

[61] T.D. Than, G. Alici, H. Zhou, W. Li, A review of localization systems for robotic

endoscopic capsules, IEEE Trans. Biomed. Eng. 59 (2012) 2387–2399. https://doi.org/10.1109/TBME.2012.2201715.

[62] H. Mateen, R. Basar, A.U. Ahmed, M.Y. Ahmad, Localization of Wireless Capsule Endoscope: A Systematic Review, IEEE Sens. J. 17 (2017) 1197–1206. https://doi.org/10.1109/JSEN.2016.2645945.

[63] G.N. Levinthal, C.A. Burke, J.M. Santisi, The accuracy of an endoscopy nurse in interpreting capsule endoscopy, Am. J. Gastroenterol. 98 (2003) 2669–2671. https://doi.org/10.1111/j.1572-0241.2003.08726.x.

[64] L.H. Lai, G.L.H. Wong, D.K.L. Chow, J.Y.W. Lau, J.J.Y. Sung, W.K. Leung, Inter-observer variations on interpretation of capsule endoscopies, Eur. J. Gastroenterol. Hepatol. 18 (2006) 283–286. https://doi.org/10.1097/00042737-200603000-00009.

[65] A. Riphaus, S. Richter, M. Vonderach, T. Wehrmann, Capsule endoscopy interpretation by an endoscopy nurse - a comparative trial., Z Gastroenterol. 47 (2009) 273–6. https://doi.org/10.1055/s-2008-1027822.

[66] H. Dokoutsidou, S. Karagiannis, E. Giannakoulopoulou, P. Galanis, N. Kyriakos, C. Liatsos, S. Faiss, C. Mavrogiannis, A study comparing an endoscopy nurse and an endoscopy physician in capsule endoscopy interpretation, Eur. J. Gastroenterol. Hepatol. 23 (2011) 166–170. https://doi.org/10.1097/MEG.0b013e3283433abf.

[67] M. Alagappan, J.R.G. Brown, Y. Mori, T.M. Berzin, Artificial intelligence in gastrointestinal endoscopy: The future is almost here, World J. Gastrointest. Endosc. 10 (2018) 239–249. https://doi.org/10.4253/wjge.v10.i10.239.

[68] C. Le Berre, W.J. Sandborn, S. Aridhi, M.-D. Devignes, L. Fournier, M. Smaïl-Tabbone, S. Danese, L. Peyrin-Biroulet, Application of Artificial Intelligence to Gastroenterology and Hepatology, Gastroenterology. 158 (2020) 76-94.e2. https://doi.org/10.1053/j.gastro.2019.08.058.

[69] H. Lennernäs, Ö. Ahrenstedt, R. Hällgren, L. Knutson, M. Ryde, L.K. Paalzow, Regional Jejunal Perfusion, a New in Vivo Approach to Study Oral Drug Absorption in Man, Springer, 1992. https://doi.org/10.1023/A:1015888813741.

[70] N. Rouge, P. Buri, E. Doelker, Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery, Int. J. Pharm. 136 (1996) 117–139. https://doi.org/10.1016/0378-5173(96)85200-8.

[71] F. Munoz, G. Alici, W. Li, A review of drug delivery systems for capsule endoscopy, Adv. Drug Deliv. Rev. 71 (2014) 77–85. https://doi.org/10.1016/j.addr.2013.12.007.

[72] R. Gröning, Computer-controlled drug release from small-sized dosage forms, J. Control. Release. 48 (1997) 185–193. https://doi.org/10.1016/S0168-3659(97)00044-8.

[73] A. Horst Staib, D. Beermann, S. Harder, U. Fuhr, D. Liermann, Absorption differences of ciprofloxacin along the human gastrointestinal tract determined using a remote-control drug delivery device (HF-capsule), Am. J. Med. (1989). https://doi.org/10.1016/0002-9343(89)90026-0.

[74] S. Harder, U. Fuhr, D. Beermann, A. Staib, Ciprofloxacin absorption in different regions of the human gastrointestinal tract. Investigations with the hf-capsule., Br. J. Clin. Pharmacol. (1990). https://doi.org/10.1111/j.1365-2125.1990.tb03740.x.

[75] A.H. Staib, D. Loew, S. Harder, E.H. Graul, R. Pfab, Measurement of theophylline absorption from different regions of the gastro-intestinal tract using a remote controlled durg delivery device, Eur. J. Clin. Pharmacol. (1986). https://doi.org/10.1007/BF00608217.

[76] O. Schuster, B. Hugemann, Course of Development of the HF-Capsule — Variations and Method-Related Typical Findings, in: Drug Absorpt. Differ. Reg. Hum. Gastro-Intestinal Tract Methods Investig. Results / Arzneimittelabsorption Aus Verschied.

Bereichen Des Gastrointestinaltraktes Beim Menschen Untersuchungsmethoden Und Ergebnisse, Vieweg+Teubner Verlag, Wiesbaden, 1987: pp. 28–38. https://doi.org/10.1007/978-3-322-91091-2_5.

[77] D. V. Prior, A.L. Connor, I.R. Wilding, The Enterion Capsule, in: M.J. Rathbone, J. Hadgraft, M.S. Roberts (Eds.), Modif. Drug Deliv. Technol., Marcel Dekker Inc., 2003.

[78] A.F. Parr, E.P. Sandefer, P. Wissel, M. McCartney, C. McClain, U.Y. Ryo, G.A. Digenis, Evaluation of the feasibility and use of a prototype remote drug delivery capsule (RDDC) for non-invasive regional drug absorption studies in the GI tract of man and beagle dog, Pharm. Res. 16 (1999) 266–271. https://doi.org/10.1023/A:1018884510163.

[79] M.E.A. McGirr, S.M. McAllister, E.E. Peters, A.W. Vickers, A.F. Parr, A.W. Basit, The use of the InteliSite® Companion device to deliver mucoadhesive polymers to the dog colon, Eur. J. Pharm. Sci. 36 (2009) 386–391. https://doi.org/10.1016/j.ejps.2008.11.007.

[80] R. Gröning, Computer-controlled release of metoprolol from capsules, Int. J. Pharm. 87 (1992) 89–93. https://doi.org/10.1016/0378-5173(92)90231-P.

[81] R. Groening, H. Bensmann, High frequency controlled capsules with integrated gas producing cells, Eur. J. Pharm. Biopharm. 72 (2009) 282–284. https://doi.org/10.1016/j.ejpb.2009.01.003.

[82] D.A. Parasrampuria, T. Kanamaru, A. Connor, I. Wilding, K. Ogata, Y. Shimoto, S. Kunitada, Evaluation of regional gastrointestinal absorption of edoxaban using the enterion capsule, J. Clin. Pharmacol. 55 (2015) 1286–1292. https://doi.org/10.1002/jcph.540.

[83] S. Macha, C.-L. Yong, T.R. MacGregor, M. Castles, A.-M. Quinson, N. Rouyrre, I. Wilding, Assessment of Nevirapine Bioavailability From Targeted Sites in the Human Gastrointestinal Tract, J. Clin. Pharmacol. 49 (2009) 1417–1425.

https://doi.org/10.1177/0091270009344856.

[84] W. Byon, S. Nepal, A.E. Schuster, A. Shenker, C.E. Frost, Regional Gastrointestinal Absorption of Apixaban in Healthy Subjects, J. Clin. Pharmacol. 58 (2018) 965–971. https://doi.org/10.1002/jcph.1097.

[85] P.J. van der Schaar, F. Dijksman, J. Shimizu, C. Wanke, P.D. Siersema, First in Human Study With a Novel Ingestible Electronic Drug Delivery and Monitoring Device: The Intellicap, Gastroenterology. 140 (2018) S-766. https://doi.org/10.1016/s0016-5085(11)63178-8.

[86] J.M. Maurer, R.C.A. Schellekens, H.M. van Rieke, C. Wanke, V. Iordanov, F. Stellaard, K.D. Wutzke, G. Dijkstra, M. van der Zee, H.J. Woerdenbag, H.W. Frijlink, J.G.W. Kosterink, Gastrointestinal pH and Transit Time Profiling in Healthy Volunteers Using the IntelliCap System Confirms Ileo-Colonic Release of ColoPulse Tablets, PLoS One. 10 (2015) e0129076. https://doi.org/10.1371/journal.pone.0129076.

[87] E. Söderlind, B. Abrahamsson, F. Erlandsson, C. Wanke, V. Iordanov, C. von Corswant, Validation of the IntelliCap® system as a tool to evaluate extended release profiles in human GI tract using metoprolol as model drug, J. Control. Release. 217 (2015) 300–307. https://doi.org/10.1016/j.jconrel.2015.09.024.

[88] D. Becker, J. Zhang, T. Heimbach, R.C. Penland, C. Wanke, J. Shimizu, K. Kulmatycki, Novel Orally Swallowable IntelliCap® Device to Quantify Regional Drug Absorption in Human GI Tract Using Diltiazem as Model Drug, AAPS PharmSciTech. 15 (2014) 1490–1497. https://doi.org/10.1208/s12249-014-0172-1.

[89] D. Miller, R. Niichel, ADVANCING HIGH TECH DRUG DELIVERY SYSTEMS FOR THE TREATMENT OF CROHN'S DISEASE, Inflamm. Bowel Dis. 27 (2021) S2–S2. https://doi.org/10.1093/ibd/izaa347.003.

[90] A.C. Anselmo, Y. Gokarn, S. Mitragotri, Non-invasive delivery strategies for biologics,

Nat. Rev. Drug Discov. 18 (2018) 19–40. https://doi.org/10.1038/nrd.2018.183.

[91] M. Durán-Lobato, Z. Niu, M.J. Alonso, Oral Delivery of Biologics for Precision Medicine, Adv. Mater. 32 (2020) 1901935. https://doi.org/10.1002/adma.201901935.

[92] H.L. Quinn, M.C. Kearney, A.J. Courtenay, M.T. McCrudden, R.F. Donnelly, The role of microneedles for drug and vaccine delivery, Expert Opin. Drug Deliv. 11 (2014) 1769–1780. https://doi.org/10.1517/17425247.2014.938635.

[93] E. Larrañeta, M.T.C. McCrudden, A.J. Courtenay, R.F. Donnelly, Microneedles: A New Frontier in Nanomedicine Delivery, Pharm. Res. 33 (2016) 1055–1073. https://doi.org/10.1007/s11095-016-1885-5.

[94] G. Traverso, C.M. Schoellhammer, A. Schroeder, R. Maa, G.Y. Lauwers, B.E. Polat, D.G. Anderson, D. Blankschtein, R. Langer, Microneedles for Drug Delivery via the Gastrointestinal Tract, J. Pharm. Sci. 104 (2015) 362–367. https://doi.org/10.1002/jps.24182.

[95] A. Abramson, E. Caffarel-Salvador, V. Soares, D. Minahan, R.Y. Tian, X. Lu, D. Dellal, Y. Gao, S. Kim, J. Wainer, J. Collins, S. Tamang, A. Hayward, T. Yoshitake, H.-C. Lee, J. Fujimoto, J. Fels, M.R. Frederiksen, U. Rahbek, N. Roxhed, R. Langer, G. Traverso, A luminal unfolding microneedle injector for oral delivery of macromolecules, Nat. Med. 25 (2019) 1512–1518. https://doi.org/10.1038/s41591-019-0598-9.

[96] M. Hashim, R. Korupolu, B. Syed, K. Horlen, S. Beraki, P. Karamchedu, A.K. Dhalla, R. Ruffy, M. Imran, Jejunal wall delivery of insulin via an ingestible capsule in anesthetized swine—A pharmacokinetic and pharmacodynamic study, Pharmacol. Res. Perspect. 7 (2019). https://doi.org/10.1002/prp2.522.

[97] A.K. Dhalla, Z. Al-Shamsie, S. Beraki, A. Dasari, L.C. Fung, L. Fusaro, A. Garapaty, B. Gutierrez, D. Gratta, M. Hashim, K. Horlen, P. Karamchedu, R. Korupolu, E. Liang, C. Ong, Z. Owyang, V. Salgotra, S. Sharma, B. Syed, M. Syed, A.T. Vo, R. Abdul-Wahab,

A. Wasi, A. Yamaguchi, S. Yen, M. Imran, A robotic pill for oral delivery of biotherapeutics: safety, tolerability, and performance in healthy subjects, Drug Deliv. Transl. Res. (2021) 1–12. https://doi.org/10.1007/s13346-021-00938-1.

[98] M. Camović, A. Biščević, I. Brčić, K. Borčak, S. Bušatlić, N. Ćenanović, A. Dedović, A. Mulalić, M. Sirbubalo, A. Tucak, E. Vranić, Acid-Resistant Capsules with Sugar Microneedles for Oral Delivery of Ascorbic Acid, in: Proc. Int. Conf. Med. Biol. Eng. 2019, Springer, Banja Luka, Bosnia and Herzegovina, Bosnia and Herzegovina, 2020: pp. 749–753. https://doi.org/10.1007/978-3-030-17971-7_111.

[99] T.R.R. Singh, H. Mcmillan, K. Mooney, A.Z. Alkilani, R.F. Donnelly, Microneedles for drug delivery and monitoring, in: Microfluid. Devices Biomed. Appl., Elsevier Inc., 2013: pp. 185–230. https://doi.org/10.1533/9780857097040.2.185.

[100] N.G. Velitchkov, G.I. Grigorov, J.E. Losanoff, K.T. Kjossev, Ingested foreign bodies of the gastrointestinal tract: Retrospective analysis of 542 cases, in: World J. Surg., Springer, 1996: pp. 1001–1005. https://doi.org/10.1007/s002689900152.

[101] R. Castro, D. Libânio, I. Pita, M. Dinis-Ribeiro, Solutions for submucosal injection: What to choose and how to do it, World J. Gastroenterol. 25 (2019) 777–788. https://doi.org/10.3748/wjg.v25.i7.777.

[102] D. Yamaguchi, H. Yoshida, K. Ikeda, Y. Takeuchi, S. Yamashita, A. Jubashi, T. Yukimoto, E. Takeshita, W. Yoshioka, H. Fukuda, N. Tominaga, N. Tsuruoka, T. Morisaki, K. Ario, S. Tsunada, K. Fujimoto, Colorectal endoscopic mucosal resection with submucosal injection of epinephrine versus hypertonic saline in patients taking antithrombotic agents: propensity-score-matching analysis, BMC Gastroenterol. 19 (2019) 192. https://doi.org/10.1186/s12876-019-1114-x.

[103] S. Ghosh, D. Watts, M. Kinnear, Management of gastrointestinal haemorrhage, Postgrad. Med. J. 78 (2002) 4–14. https://doi.org/10.1136/pmj.78.915.4.

[104] S.M. Bal, J. Caussin, S. Pavel, J.A. Bouwstra, In vivo assessment of safety of microneedle arrays in human skin, Eur. J. Pharm. Sci. 35 (2008) 193–202. https://doi.org/10.1016/j.ejps.2008.06.016.

[105] E. Husebye, The patterns of small bowel motility: physiology and implications in organic disease and functional disorders, Neurogastroenterol. Motil. 11 (1999) 141–161. https://doi.org/10.1046/j.1365-2982.1999.00147.x.

[106] A. Abramson, E. Caffarel-Salvador, M. Khang, D. Dellal, D. Silverstein, Y. Gao, M.R. Frederiksen, A. Vegge, F. Hubálek, J.J. Water, A. V. Friderichsen, J. Fels, R.K. Kirk, C. Cleveland, J. Collins, S. Tamang, A. Hayward, T. Landh, S.T. Buckley, N. Roxhed, U. Rahbek, R. Langer, G. Traverso, An ingestible self-orienting system for oral delivery of macromolecules, Science (80-.). 363 (2019) 611–615. https://doi.org/10.1126/science.aau2277.

[107] M. Scudellari, Shot to the Gut: “Robotic” Pill Sails Through Human Safety Study, IEEE Spectr. (2019). https://spectrum.ieee.org/the-human-os/biomedical/devices/shot-to-the-gut-robotic-pill-sails-through-human-safety-study (accessed April 27, 2020).

[108] RANI Therapeutics, A First-in-Human Study of Enteral Drug Delivery Device, Clin. Trials.Gov. (n.d.). https://clinicaltrials.gov/ct2/show/NCT03798912 (accessed March 19, 2020).

[109] S. Melmed, V. Popovic, M. Bidlingmaier, M. Mercado, A.J. van der Lely, N. Biermasz, M. Bolanowski, M. Coculescu, J. Schopohl, K. Racz, B. Glaser, M. Goth, Y. Greenman, P. Trainer, E. Mezosi, I. Shimon, A. Giustina, M. Korbonits, M.D. Bronstein, D. Kleinberg, S. Teichman, I. Gliko-Kabir, R. Mamluk, A. Haviv, C. Strasburger, Safety and Efficacy of Oral Octreotide in Acromegaly: Results of a Multicenter Phase III Trial, J. Clin. Endocrinol. Metab. 100 (2015) 1699–1708. https://doi.org/10.1210/jc.2014-4113.

[110] S. Sarker, B. Wankum, J. Shimizu, R. Jones, B.S. Terry, A Factorial Approach for Optimizing the Design Parameters of a Tissue Attachment Mechanism for Drug

Delivery, IEEE Trans. Biomed. Eng. (2021) 1–1. https://doi.org/10.1109/TBME.2021.3086975.

[111] J. Lee, H. Lee, S. hyun Kwon, S. Park, Active delivery of multi-layer drug-loaded microneedle patches using magnetically driven capsule, Med. Eng. Phys. 85 (2020) 87–96. https://doi.org/10.1016/j.medengphy.2020.09.012.

[112] W. Xie, W.M. Lewis, J. Kaser, C. Ross Welch, P. Li, C.A. Nelson, V. Kothari, B.S. Terry, Design and Validation of a Biosensor Implantation Capsule Robot, J. Biomech. Eng. 139 (2017). https://doi.org/10.1115/1.4036607.

[113] C.M. Schoellhammer, A. Schroeder, R. Maa, G.Y. Lauwers, A. Swiston, M. Zervas, R. Barman, A.M. DiCiccio, W.R. Brugge, D.G. Anderson, D. Blankschtein, R. Langer, G. Traverso, Ultrasound-mediated gastrointestinal drug delivery, Sci. Transl. Med. 7 (2015) 310ra168-310ra168. https://doi.org/10.1126/scitranslmed.aaa5937.

[114] C.M. Schoellhammer, R. Langer, G. Traverso, Of microneedles and ultrasound: Physical modes of gastrointestinal macromolecule delivery, Tissue Barriers. 4 (2016) e1150235. https://doi.org/10.1080/21688370.2016.1150235.

[115] F. Stewart, G. Cummins, M. V. Turcanu, B.F. Cox, A. Prescott, E. Clutton, I.P. Newton, M.P.Y. Desmulliez, M. Thanou, H. Mulvana, S. Cochran, I. Näthke, Ultrasound mediated delivery of quantum dots from a proof of concept capsule endoscope to the gastrointestinal wall, Sci. Rep. 11 (2021) 2584. https://doi.org/10.1038/s41598-021-82240-1.

[116] F.R. Stewart, Y. Qiu, H.S. Lay, I.P. Newton, B.F. Cox, M.A. Al-Rawhani, J. Beeley, Y. Liu, Z. Huang, D.R.S. Cumming, I. Näthke, S. Cochran, Acoustic sensing and ultrasonic drug delivery in multimodal theranostic capsule endoscopy, Sensors. 17 (2017) 1553. https://doi.org/10.3390/s17071553.

[117] F. Stewart, A. Verbeni, Y. Qiu, B.F. Cox, J. Vorstius, I.P. Newton, Z. Huang, A.

Menciassi, I. Näthke, S. Cochran, A Prototype Therapeutic Capsule Endoscope for Ultrasound-Mediated Targeted Drug Delivery, J. Med. Robot. Res. 03 (2018) 1840001. https://doi.org/10.1142/S2424905X18400019.

[118] L. Bisset, Y.E. Cossart, W. Selby, R. West, D. Catterson, K. O'Hara, K. Vickery, A prospective study of the efficacy of routine decontamination for gastrointestinal endoscopes and the risk factors for failure, Am. J. Infect. Control. 34 (2006) 274–280. https://doi.org/10.1016/J.AJIC.2005.08.007.

[119] N. Kenters, E.G.W. Huijskens, C. Meier, A. Voss, Infectious diseases linked to cross-contamination of flexible endoscopes, Endosc. Int. Open. 3 (2015) E259. https://doi.org/10.1055/S-0034-1392099.

[120] B. Lambert, J. Martin, Sterilization of Implants and Devices, in: Biomater. Sci., Elsevier, 2013: pp. 1339–1353. https://doi.org/10.1016/B978-0-08-087780-8.00125-X.

[121] L. Osterberg, T. Blaschke, Adherence to Medication, N. Engl. J. Med. 353 (2005) 487–497. https://doi.org/10.1056/NEJMra050100.

[122] P.J. McDonnell, M.R. Jacobs, Hospital Admissions Resulting from Preventable Adverse Drug Reactions, Ann. Pharmacother. 36 (2002) 1331–1336. https://doi.org/10.1345/aph.1A333.

[123] A. Kubica, A. Kosobucka, T. Fabiszak, D.A. Gorog, J.M. Siller-Matula, Assessment of adherence to medication in patients after myocardial infarction treated with percutaneous coronary intervention. Is there a place for newself-reported questionnaires?, Curr. Med. Res. Opin. 35 (2019) 341–349. https://doi.org/10.1080/03007995.2018.1510385.

[124] M. Viswanathan, C.E. Golin, C.D. Jones, M. Ashok, S.J. Blalock, R.C.M. Wines, E.J.L. Coker-Schwimmer, D.L. Rosen, P. Sista, K.N. Lohr, Interventions to Improve Adherence to Self-administered Medications for Chronic Diseases in the United States,

Ann. Intern. Med. 157 (2012) 785. https://doi.org/10.7326/0003-4819-157-11-201212040-00538.

[125] World Health Organisation, Adherence to Long-Term Therapies - Evidence for Action, Geneva, 2003. https://apps.who.int/iris/bitstream/handle/10665/42682/9241545992.pdf.

[126] E. Vermeire, H. Hearnshaw, P. Van Royen, J. Denekens, Patient adherence to treatment: three decades of research. A comprehensive review, J. Clin. Pharm. Ther. 26 (2001) 331–342. https://doi.org/10.1046/j.1365-2710.2001.00363.x.

[127] R. Nieuwlaat, N. Wilczynski, T. Navarro, N. Hobson, R. Jeffery, A. Keepanasseril, T. Agoritsas, N. Mistry, A. Iorio, S. Jack, B. Sivaramalingam, E. Iserman, R.A. Mustafa, D. Jedraszewski, C. Cotoi, R.B. Haynes, Interventions for enhancing medication adherence, Cochrane Database Syst. Rev. 2014 (2014). https://doi.org/10.1002/14651858.CD000011.pub4.

[128] R.L. Ailinger, P.L. Black, N. Lima-Garcia, Use of electronic monitoring in clinical nursing research, Clin. Nurs. Res. 17 (2008) 89–97. https://doi.org/10.1177/1054773808316941.

[129] K. Bruxvoort, C. Festo, M. Cairns, A. Kalolella, F. Mayaya, S.P. Kachur, D. Schellenberg, C. Goodman, Measuring Patient Adherence to Malaria Treatment: A Comparison of Results from Self-Report and a Customised Electronic Monitoring Device, PLoS One. 10 (2015) e0134275. https://doi.org/10.1371/journal.pone.0134275.

[130] H. Hafezi, T.L. Robertson, G.D. Moon, K.Y. Au-Yeung, M.J. Zdeblick, G.M. Savage, An ingestible sensor for measuring medication adherence, IEEE Trans. Biomed. Eng. 62 (2015) 99–109. https://doi.org/10.1109/TBME.2014.2341272.

[131] G.P. Flores, T.C. Carnes, S.L. Baumgartner, D. Eric Buffkin, N.R. Euliano, L.N. SMITH, Performance, reliability, usability, and safety of the id-cap system for ingestion event

monitoring in healthy volunteers: A pilot study, Innov. Clin. Neurosci. 13 (2016) 12–19. /pmc/articles/PMC5141592/ (accessed February 23, 2021).

[132] Food and Drug Administration, Evaluation of automatic Class III designation (de novo) for Proteus personal monitor including ingestion event marker, 2012. https://www.accessdata.fda.gov/cdrh_docs/reviews/K113070.pdf.

[133] Otsuka Pharmaceuticals, Ablify MyCite Website, (n.d.). https://www.abilifymycite.com/ (accessed February 24, 2021).

[134] R.S. Plowman, T. Peters-Strickland, G.M. Savage, Digital medicines: clinical review on the safety of tablets with sensors, Expert Opin. Drug Saf. 17 (2018) 849–852. https://doi.org/10.1080/14740338.2018.1508447.

[135] K. Au-Yeung, G. Moon, T. Robertson, L. DiCarlo, M. Epstein, S.E. Weis, R.R. Reves, G. Engel, Early Clinical Experience With Networked System for Promoting Patient Self-Management | AJMC, Am. J. Manag. Care. 17 (2011) e277-87. https://www.ajmc.com/view/ajmc_11jul__au_yeung_e277to287 (accessed February 23, 2021).

[136] P.R. Chai, G. Goodman, M.J. Bustamante, Y. Mohamed, J. Castillo-Mancilla, E.W. Boyer, K.H. Mayer, R.K. Rosen, S.L. Baumgartner, E. Buffkin, C. O'Cleirigh, Long-Term Stability of the Electronic Sensor Component of a Digital Pill System in Real-World Storage Settings, J. Pharm. Technol. (2021) 875512252098521. https://doi.org/10.1177/8755122520985219.

[137] P.R. Chai, J. Castillo-Mancilla, E. Buffkin, C. Darling, R.K. Rosen, K.J. Horvath, E.D. Boudreaux, G.K. Robbins, P.L. Hibberd, E.W. Boyer, Utilizing an Ingestible Biosensor to Assess Real-Time Medication Adherence, J. Med. Toxicol. 11 (2015) 439–444. https://doi.org/10.1007/s13181-015-0494-8.

[138] H. Liu, E. Daar, Y. Wang, L. Siqueiros, K. Campbell, J. Shen, M. Guerrero, M.-W.W.

Ko, D. Xiong, J. Dao, T. Young, M. Rosen, C. V. Fletcher, Pharmacokinetics of Coencapsulated Antiretrovirals with Ingestible Sensors, AIDS Res. Hum. Retroviruses. 36 (2020) 65–74. https://doi.org/10.1089/aid.2019.0202.

[139] M. Sulkowski, A.F. Luetkemeyer, D.L. Wyles, C. Martorell, A. Muir, I. Weisberg, S.C. Gordon, R. McLain, G. Huhn, Impact of a digital medicine programme on hepatitis C treatment adherence and efficacy in adults at high risk for non-adherence, Aliment. Pharmacol. Ther. 51 (2020) 1384–1396. https://doi.org/10.1111/apt.15707.

[140] S.H. Browne, A. Umlauf, A.J. Tucker, J. Low, K. Moser, J. Gonzalez Garcia, C.A. Peloquin, T. Blaschke, F. Vaida, C.A. Benson, Wirelessly observed therapy compared to directly observed therapy to confirm and support tuberculosis treatment adherence: A randomized controlled trial, PLOS Med. 16 (2019) e1002891. https://doi.org/10.1371/journal.pmed.1002891.

[141] J. Frias, N. Virdi, P. Raja, Y. Kim, G. Savage, L. Osterberg, Effectiveness of Digital Medicines to Improve Clinical Outcomes in Patients with Uncontrolled Hypertension and Type 2 Diabetes: Prospective, Open-Label, Cluster-Randomized Pilot Clinical Trial, J. Med. Internet Res. 19 (2017) e246. https://doi.org/10.2196/jmir.7833.

[142] L. Cosgrove, I.A. Cristea, A.F. Shaughnessy, B. Mintzes, F. Naudet, Digital aripiprazole or digital evergreening? A systematic review of the evidence and its dissemination in the scientific literature and in the media, BMJ Evidence-Based Med. 24 (2019) 231–238. https://doi.org/10.1136/bmjebm-2019-111204.

[143] A. Alipour, S. Gabrielson, P.B. Patel, Ingestible Sensors and Medication Adherence: Focus on Use in Serious Mental Illness, Pharmacy. 8 (2020) 103. https://doi.org/10.3390/pharmacy8020103.

[144] R. Belknap, S. Weis, A. Brookens, K.Y. Au-Yeung, G. Moon, L. DiCarlo, R. Reves, Feasibility of an Ingestible Sensor-Based System for Monitoring Adherence to Tuberculosis Therapy, PLoS One. 8 (2013) e53373.

https://doi.org/10.1371/journal.pone.0053373.

[145] P.R. Chai, S. Carreiro, B.J. Innes, B. Chapman, K.L. Schreiber, R.R. Edwards, A.W. Carrico, E.W. Boyer, Oxycodone Ingestion Patterns in Acute Fracture Pain With Digital Pills, Anesth. Analg. 125 (2017) 2105–2112. https://doi.org/10.1213/ANE.0000000000002574.

[146] A.P. Kencana, M. Rasouli, V.A. Huynh, E.K. Ting, J.V.Y. Lai, Q.D.Q. Huy, S.L. Tan, K.J. Wong, S.J. Phee, An ingestible wireless capsule for treatment of obesity, 2010 Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBC'10. (2010) 963–966. https://doi.org/10.1109/IEMBS.2010.5627585.

[147] L. Yan, T. Wang, D. Liu, J. Peng, Z. Jiao, C.Y. Chen, Capsule robot for obesity treatment with wireless powering and communication, IEEE Trans. Ind. Electron. 62 (2015) 1125–1133. https://doi.org/10.1109/TIE.2014.2352216.

[148] T.N. Do, T.E.T. Seah, H.K. Yu, S.J. Phee, Development and Testing of a Magnetically Actuated Capsule Endoscopy for Obesity Treatment, PLoS One. 11 (2016) e0148035. https://doi.org/10.1371/journal.pone.0148035.

[149] T.N. Do, P.T. Phan, K.Y. Ho, S.J. Phee, A magnetic soft endoscopic capsule for non-surgical overweight and obese treatments, IEEE Int. Conf. Intell. Robot. Syst. 2016-Novem (2016) 2388–2393. https://doi.org/10.1109/IROS.2016.7759372.

[150] H.L. Kaan, P.T. Phan, A.M.H. Tiong, M. Miyasaka, S.J. Phee, K.Y. Ho, First-in-man feasibility study of a novel ingestible magnetically inflated balloon capsule for treatment of obesity, Endosc. Int. Open. 08 (2020) E607–E610. https://doi.org/10.1055/a-1127-2991.

[151] T.N. Do, K.Y. Ho, S.J. Phee, A Magnetic Soft Endoscopic Capsule-Inflated Intragastric Balloon for Weight Management, Sci. Rep. 6 (2016) 39486. https://doi.org/10.1038/srep39486.

[152] P.T. Phan, A.M.H. Tiong, M. Miyasaka, L. Cao, H.L. Kaan, K.Y. Ho, S.J. Phee, EndoPil: A Magnetically Actuated Swallowable Capsule for Weight Management: Development and Trials, Ann. Biomed. Eng. (2020). https://doi.org/10.1007/s10439-020-02692-w.

[153] S.H. Kim, H.J. Chun, H.S. Choi, E.S. Kim, B. Keum, Y.T. Jeen, Current status of intragastric balloon for obesity treatment, World J. Gastroenterol. 22 (2016) 5495. https://doi.org/10.3748/wjg.v22.i24.5495.

[154] O. Gyring Nieben, H. Harboe, Intragastric Balloon as an artifical bezoar for treatment of obesity, Lancet. 319 (1982) 198–199. https://doi.org/10.1016/S0140-6736(82)90762-0.

[155] J. Ponce, B.B. Quebbemann, E.J. Patterson, Prospective, randomized, multicenter study evaluating safety and efficacy of intragastric dual-balloon in obesity, Surg. Obes. Relat. Dis. 9 (2013) 290–295. https://doi.org/10.1016/j.soard.2012.07.007.

[156] I. Imaz, C. Martínez-Cervell, E.E. García-Álvarez, J.M. Sendra-Gutiérrez, J. González-Enríquez, Safety and effectiveness of the intragastric balloon for obesity. A meta-analysis, Obes. Surg. 18 (2008) 841–846. https://doi.org/10.1007/s11695-007-9331-8.

[157] A. Nag, S.A. Martin, D. Mladsi, O. Olayinka-Amao, M. Purser, R.M. Vekaria, The Humanistic and Economic Burden of Chronic Idiopathic Constipation in the USA: A Systematic Literature Review, Clin. Exp. Gastroenterol. Volume 13 (2020) 255–265. https://doi.org/10.2147/CEG.S239205.

[158] A. Sharma, S. Rao, Constipation: Pathophysiology and Current Therapeutic Approaches, in: Gastrointest. Pharmacol., 2016: pp. 59–74. https://doi.org/10.1007/164_2016_111.

[159] A. WALD, C. SCARPIGNATO, M.A. KAMM, S. MUELLER-LISSNER, I. HELFRICH, C. SCHUIJT, J. BUBECK, C. LIMONI, O. PETRINI, The burden of constipation on quality of life: results of a multinational survey, Aliment. Pharmacol. Ther. 26 (2007) 227–236.

https://doi.org/10.1111/j.1365-2036.2007.03376.x.

[160] B.E. Lacy, E.P. Shea, M. Manuel, J.L. Abel, H. Jiang, D.C.A. Taylor, Lessons learned: Chronic idiopathic constipation patient experiences with over-the-counter medications, PLoS One. 16 (2021) e0243318. https://doi.org/10.1371/journal.pone.0243318.

[161] Y. Ron, Z. Halpern, R. Safadi, R. Dickman, R. Dekel, A.D. Sperber, Safety and efficacy of the vibrating capsule, an innovative non-pharmacological treatment modality for chronic constipation, Neurogastroenterol. Motil. 27 (2015) 99–104. https://doi.org/10.1111/nmo.12485.

[162] A.D. Nelson, M. Camilleri, A. Acosta, A. Boldingh, I. Busciglio, D. Burton, M. Ryks, A.R. Zinsmeister, A single-center, prospective, double-blind, sham-controlled, randomized study of the effect of a vibrating capsule on colonic transit in patients with chronic constipation, Neurogastroenterol. Motil. 29 (2017) e13034. https://doi.org/10.1111/nmo.13034.

[163] S.S.C. Rao, A. Lembo, W.D. Chey, K. Friedenberg, E.M.M. Quigley, Effects of the vibrating capsule on colonic circadian rhythm and bowel symptoms in chronic idiopathic constipation, Neurogastroenterol. Motil. 32 (2020). https://doi.org/10.1111/nmo.13890.

[164] T.F. Cutts, J. Luo, W. Starkebaum, H. Rashed, T.L. Abell, Is gastric electrical stimulation superior to standard pharmacologic therapy in improving GI symptoms, healthcare resources, and long-term health care benefits?, Neurogastroenterol. Motil. 17 (2005) 35–43. https://doi.org/10.1111/j.1365-2982.2004.00609.x.

[165] T.L. Abell, G. Yamada, R.W. McCallum, M.L. Van Natta, J. Tonascia, H.P. Parkman, K.L. Koch, I. Sarosiek, G. Farrugia, M. Grover, W. Hasler, L. Nguyen, W. Snape, B. Kuo, R. Shulman, F.A. Hamilton, P.J. Pasricha, Effectiveness of gastric electrical stimulation in gastroparesis: Results from a large prospectively collected database of national gastroparesis registries, Neurogastroenterol. Motil. 31 (2019). https://doi.org/10.1111/nmo.13714.

[166] A. Maisiyiti, J.D. Chen, Systematic review on gastric electrical stimulation in obesity treatment, Expert Rev. Med. Devices. 16 (2019) 855–861. https://doi.org/10.1080/17434440.2019.1673728.

[167] A. Abramson, D. Dellal, Y.L. Kong, J. Zhou, Y. Gao, J. Collins, S. Tamang, J. Wainer, R. McManus, A. Hayward, M.R. Frederiksen, J.J. Water, B. Jensen, N. Roxhed, R. Langer, G. Traverso, Ingestible transiently anchoring electronics for microstimulation and conductive signaling, Sci. Adv. 6 (2020) eaaz0127. https://doi.org/10.1126/sciadv.aaz0127.

[168] S. Liu, S. Chu, L.A. Beardslee, R. Ghodssi, Hybrid and Passive Tissue-Anchoring Mechanism for Ingestible Resident Devices, J. Microelectromechanical Syst. 29 (2020) 706–712. https://doi.org/10.1109/JMEMS.2020.2999448.

[169] W. Xie, V. Kothari, B.S. Terry, A bio-inspired attachment mechanism for long-term adhesion to the small intestine, Biomed. Microdevices. 17 (2015) 68. https://doi.org/10.1007/s10544-015-9972-7.

[170] H. Zhou, G. Alici, A Novel Magnetic Anchoring System for Wireless Capsule Endoscopes Operating within the Gastrointestinal Tract, IEEE/ASME Trans. Mechatronics. 24 (2019) 1106–1116. https://doi.org/10.1109/TMECH.2019.2909288.

[171] H. Zhou, G. Alici, F. Munoz, A magnetically actuated anchoring system for a wireless endoscopic capsule, Biomed. Microdevices. 18 (2016) 1–9. https://doi.org/10.1007/s10544-016-0129-0.

[172] M.E. Karagozler, E. Cheung, J. Kwon, M. Sitti, Miniature endoscopie capsule robot using biomimetic micro-patterned adhesives, Proc. First IEEE/RAS-EMBS Int. Conf. Biomed. Robot. Biomechatronics, 2006, BioRob 2006. 2006 (2006) 105–111. https://doi.org/10.1109/BIOROB.2006.1639068.

[173] E. Cheung, M.E. Karagozler, S. Park, B. Kim, M. Sitti, A new endoscopic microcapsule

robot using beetle inspired microfibrillar adhesives, IEEE/ASME Int. Conf. Adv. Intell. Mechatronics, AIM. 1 (2005) 551–557. https://doi.org/10.1109/aim.2005.1511040.

[174] C. Steiger, A. Abramson, P. Nadeau, A.P. Chandrakasan, R. Langer, G. Traverso, Ingestible electronics for diagnostics and therapy, Nat. Rev. Mater. 4 (2019) 83–98. https://doi.org/10.1038/s41578-018-0070-3.

[175] W.H. Crosby, U.S. Army, H.W. Kugler, Intraluminal biopsy of the small intestine, Am. J. Dig. Dis. 2 (1957) 236–241. https://doi.org/10.1007/BF02231100.

[176] H.L. Greene, N.S. Rosensweig, E.G. Lufkin, L. Hagler, D. Gozansky, O.D. Taunton, R.H. Herman, Biopsy of the small intestine with the Crosby-Kugler capsule - Experience in 3,866 peroral biopsies in children and adults, Am. J. Dig. Dis. 19 (1974) 189–198. https://doi.org/10.1007/BF01072534.

[177] S.W. Clarke, JEJUNAL PERFORATION WITH THE CROSBY CAPSULE, Lancet. 284 (1964) 727–728. https://doi.org/10.1016/S0140-6736(64)92545-0.

[178] M. VIDINLI, J.M. FINLAY, MASSIVE HEMORRHAGE FOLLOWING SMALL BOWEL BIOPSY., Can. Med. Assoc. J. 91 (1964) 1223–1225. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1928509/ (accessed March 15, 2021).

[179] S.N. Salem, R.H. Salt, S.C. Truelove, Crosby small-intestinal capsule with radio-opaque tube and latex sheath, Gut. 6 (1965) 99–100. https://doi.org/10.1136/gut.6.1.99.

[180] M. Hoang, V. Le, K. Nguyen, V. Nguyen, J. Kim, E. Choi, S. Bang, B. Kang, J.-O. Park, C.-S. Kim, A Robotic Biopsy Endoscope with Magnetic 5-DOF Locomotion and a Retractable Biopsy Punch, Micromachines. 11 (2020) 98. https://doi.org/10.3390/mi11010098.

[181] D. Son, H. Gilbert, M. Sitti, Magnetically Actuated Soft Capsule Endoscope for Fine-Needle Biopsy, Soft Robot. 7 (2020) 10–21. https://doi.org/10.1089/soro.2018.0171.

[182] M.C. Hoang, V.H. Le, J. Kim, E. Choi, B. Kang, J.-O. Park, C.-S. Kim, Untethered Robotic Motion and Rotating Blade Mechanism for Actively Locomotive Biopsy Capsule Endoscope, IEEE Access. 7 (2019) 93364–93374. https://doi.org/10.1109/ACCESS.2019.2927894.

[183] Sehyuk Yim, E. Gultepe, D.H. Gracias, M. Sitti, Biopsy using a Magnetic Capsule Endoscope Carrying, Releasing, and Retrieving Untethered Microgrippers, IEEE Trans. Biomed. Eng. 61 (2014) 513–521. https://doi.org/10.1109/TBME.2013.2283369.

[184] M. Simi, G. Gerboni, A. Menciassi, P. Valdastri, Magnetic Torsion Spring Mechanism for a Wireless Biopsy Capsule, J. Med. Device. 7 (2013) 041009. https://doi.org/10.1115/1.4025185.

[185] K. Kong, S. Yim, S. Choi, D. Jeon, A Robotic Biopsy Device for Capsule Endoscopy, J. Med. Device. 6 (2012). https://doi.org/10.1115/1.4007100.

[186] D.O. Otuya, Y. Verma, H. Farrokhi, L. Higgins, M. Rosenberg, C. Damman, G.J. Tearney, Non-endoscopic biopsy techniques: a review, Expert Rev. Gastroenterol. Hepatol. 12 (2018) 109–117. https://doi.org/10.1080/17474124.2018.1412828.

[187] F. Guarner, J.-R.J.J.-R. Malagelada, G. Simon, S. Gorbach, S. Borriello, S. Bengmark, M. Levison, A. Stephen, J. Cummings, S. Salminen, C. Bouley, M. Bouton-Ruault, E. Al., S. Long, R. Swenson, H. Yoshioka, K. Iseki, K. Fujita, H. Harmsen, A. Wildeboer-Veloo, G. Raangs, E. Al., M. Gronlund, O. Lehtonen, E. Eerola, P. Kero, A. Simhon, J. Douglas, B. Drasar, J. Soothill, B. Lundequist, C. Nord, J. Winberg, I. Adlerberth, B. Carlsson, P. de Man, E. Al., L. Hooper, M. Wong, A. Thelin, L. Hansson, P. Falk, J. Gordon, R. Ducluzeau, W. Moore, L. Moore, K. Wilson, R. Blitchington, A. Suau, R. Bonnet, M. Sutren, E. Al., G. Tannock, K. Kimura, A. McCartney, M. McConnell, G. Tannock, A. Sghir, G. Gramet, A. Suau, V. Rochet, P. Pochart, J. Dore, A. Franks, H. Harmsen, G. Raangs, G. Jansen, F. Schut, G. Welling, P. Marteau, P. Rochart, J. Dore, C. Bera-Maillet, A. Bernalier, G. Corthier, P. Falk, L. Hooper, T. Midtvedt, J. Gordon, M.

Roberfroid, F. Bornet, C. Bouley, J. Cummings, J. Cummings, E. Pomare, W. Branch, C. Naylor, G. Macfarlane, J. Cummings, E. Beatty, S. Kingman, S. Bingham, H. Englyst, G. Macfarlane, J. Cummings, C. Allison, E. Smith, G. Macfarlane, J. Cummings, H. Englyst, K. Silvester, H. Englyst, J. Cummings, J. Fallingborg, G. Macfarlane, G. Gibson, J. Cummings, J. Conly, K. Stein, L. Worobetz, S. Rutledge-Harding, M. Hill, E. Miyazawa, A. Iwabuchi, T. Yoshida, H. Younes, C. Coudray, J. Bellanger, C. Demigne, Y. Rayssiguier, C. Remesy, C. Venter, H. Vorster, J. Cummings, F. Brighenti, G. Castellani, L. Benini, E. Al., A. Thorburn, J. Muir, J. Proietto, K. Englyst, H. Englyst, G. Hudson, T. Cole, J. Cummings, J. Luo, M. Van Yperselle, S. Rizkalla, F. Rossi, F. Bornet, G. Slama, M. Alam, T. Midtvedt, A. Uribe, J. Gordon, L. Hooper, M. McNevin, M. Wong, L. Bry, W. Frankel, W. Zhang, A. Singh, E. Al., S. Siavoshian, J. Segain, M. Kornprobst, E. Al., P. Gibson, I. Moeller, O. Kagelari, M. Folino, G. Young, P. Brandtzaeg, T. Halstensen, K. Kett, E. Al., J. Butler, J. Sun, P. Weber, P. Navarro, D. Francis, Y. Umesaki, H. Setoyama, S. Matsumoto, Y. Okada, L. Helgeland, J. Vaage, B. Rolstad, T. Midtvedt, P. Brandtzaeg, J. Cebra, S. Periwal, G. Lee, F. Lee, K. Shroff, H. Klaasen, P. Van der Heijden, W. Stok, E. Al., Y. Umesaki, Y. Okada, S. Matsumoto, A. Imaoka, H. Setoyama, H. Jiang, N. Bos, J. Cebra, M. Moreau, V. Gaboriau-Routhiau, N. Sudo, S. Sawamura, K. Tanaka, Y. Aiba, C. Kubo, Y. Koga, C. Krinos, M. Coyne, K. Weinacht, A. Tzianabos, D. Kasper, L. Comstock, L. Van der Waaij, P. Limburg, G. Mesander, D. van der Waaij, M. Kagnoff, L. Eckmann, A. Aderem, R. Ulevitch, N. Borruel, M. Carol, F. Casellas, E. Al., E. Baba, S. Nagaishi, T. Fukata, A. Arakawa, H. Taguchi, M. Takahashi, H. Yamaguchi, E. Al., D. van der Waaij, M. Bernet, D. Brassart, J. Neeser, A. Servin, L. Hooper, J. Xu, P. Falk, T. Midtvedt, J. Gordon, I. Brook, V. Lievin, I. Peiffer, S. Hudault, E. Al., P. Van Leeuwen, M. Boermeester, A. Houdijk, E. Al., R. Berg, S. Lichtman, C. O'Boyle, J. MacFie, C. Mitchell, D. Johnstone, P. Sagar, P. Sedman, C. Guarner, G. Soriano, C. Guarner, B. Runyon, S. Young, M. Heck, M. Sheikh, S. Bingham, J. Rafter, B. Glinghammar, R. Hughes, A. Cross, J. Pollock, S. Bingham, M. Rieger, A. Parlesak, B. Pool-Zobel, G. Rechkemmer, C. Bode, I.

Wollowski, G. Rechkemmer, B. Pool-Zobel, M. Onoue, S. Kado, Y. Sakaitani, K. Uchida, M. Morotomi, H. Horie, K. Kanazawa, M. Okada, S. Narushima, K. Itoh, A. Terada, J. Singh, A. Rivenson, M. Tomita, S. Shimamura, N. Ishibashi, B. Reddy, B. Pool-Zobel, C. Neudecker, I. Domizlaff, E. Al., L. O'Mahony, M. Feeney, S. O'Halloran, E. Al., F. Shanahan, U. Pirzer, A. Schönhaar, B. Fleischer, E. Hermann, K.M. zum Büschenfelde, A. Macpherson, U. Khoo, I. Forgacs, J. Philpott-Howard, I. Bjarnason, A. Swidsinski, A. Ladhoff, A. Pernthaler, E. Al., J. Hampe, A. Cuthbert, P. Croucher, E. Al., S. Videla, J. Vilaseca, F. Guarner, E. Al., P. Morrissey, K. Charrier, J. Taurog, J. Richardson, J. Croft, E. Al., R. Sellon, S. Tonkonogy, M. Schultz, E. Al., S. Kitajima, M. Morimoto, E. Sagara, C. Shimizu, Y. Ikeda, A. García-Lafuente, M. Antolín, F. Guarner, E. Al., M. Mourelle, A. Salas, F. Guarner, E. Crespo, A. García-Lafuente, J.-R.J.J.-R. Malagelada, G. D'Haens, K. Geboes, M. Peeters, F. Baert, F. Penninckx, P. Rutgeerts, F. Casellas, N. Borruel, M. Papo, E. Al., W. Kruis, E. Schütz, P. Fric, B. Fixa, G. Judmaiers, M. Stolte, P. Gionchetti, F. Rizzello, A. Venturi, E. Al., F. Guarner, G. Schaafsma, G. Gibson, M. Roberfroid, S. Bengmark, J. Teitelbaum, W. Walker, G. Reid, J. Burton, J. Vanderhoof, D. Whitney, D. Antonson, T. Hanner, J. Lupo, R. Young, T. Arvola, K. Laiho, S. Torkkeli, E. Al., L. McFarland, C. Surawicz, R. Greenberg, E. Al., A. Armuzzi, F. Cremonini, F. Bartolozzi, E. Al., A. D'Souza, C. Rajkumar, J. Cooke, C. Bulpitt, J. Saavedra, N. Bauman, I. Oung, J. Perman, R. Yolken, R. Oberhelman, R. Gilman, P. Sheen, E. Al., S. Raza, S. Graham, S. Allen, S. Sultana, L. Cuevas, C. Hart, A. Shornikova, I. Casas, E. Isolauri, H. Mykkanen, T. Vesikari, A. Guarino, R. Canani, M. Spagnuolo, F. Albano, L. Di Benedetto, A. Shornikova, E. Isolauri, L. Burkanova, S. Lukovnikova, T. Vesikari, C. Pedone, A. Bernabeu, E. Postaire, C. Bouley, P. Reinert, S. Guandalini, L. Pensabene, M. Zikri, E. Al., J. Kolars, M. Levitt, M. Aouji, D. Savaiano, I. Labayen, L. Forga, A. Gonzalez, I. Lenoir-Wijnkoop, R. Nutr, J. Martinez, M. de Vrese, A. Stegelmann, B. Richter, S. Fenselau, C. Laue, J. Shrezenmeir, H. Majamaa, E. Isolauri, M. Saxelin, T. Vesikari, H. Link-Amster, F. Rochat, K. Saudan, O. Mignot, J. Aeschlimann, E. Schiffrin, F. Rochat, H. Link-Amster, J. Aeschlimann, A. Donnet-

Hugues, M. Kalliomaki, S. Salminen, H. Arvilommi, P. Kero, P. Koskinen, E. Isolauri, A. Burns, I. Rowland, B. Goldin, S. Gorbach, P. Marteau, P. Pochart, B. Flourie, E. Al., Y. Bouhnik, B. Flourie, C. Andrieux, N. Bisetti, F. Briet, J. Rambaud, S. Spanhaak, R. Havenaar, G. Schaafsma, J. Ballongue, C. Schumann, P. Quignon, Gut flora in health and disease, Lancet. 361 (2003) 512–519. https://doi.org/10.1016/S0140-6736(03)12489-0.

[188] I. Rangel, J. Sundin, S. Fuentes, D. Repsilber, W.M. de Vos, R.J. Brummer, The relationship between faecal-associated and mucosal-associated microbiota in irritable bowel syndrome patients and healthy subjects, Aliment. Pharmacol. Ther. 42 (2015) 1211–1221. https://doi.org/10.1111/apt.13399.

[189] E.G. Zoetendal, A. Von Wright, T. Vilpponen-Salmela, K. Ben-Amor, A.D.L. Akkermans, W.M. De Vos, Mucosa-associated bacteria in the human gastrointestinal tract are uniformly distributed along the colon and differ from the community recovered from feces, Appl. Environ. Microbiol. 68 (2002) 3401–3407. https://doi.org/10.1128/AEM.68.7.3401-3407.2002.

[190] Y. Momozawa, V. Deffontaine, E. Louis, J.F. Medrano, Characterization of bacteria in biopsies of colon and stools by high throughput sequencing of the V2 region of bacterial 16s rRNA gene in human, PLoS One. 6 (2011). https://doi.org/10.1371/journal.pone.0016952.

[191] P.B. Eckburg, E.M. Bik, C.N. Bernstein, E. Purdom, L. Dethlefsen, M. Sargent, S.R. Gill, K.E. Nelson, D.A. Relman, Microbiology: Diversity of the human intestinal microbial flora, Science (80-.). 308 (2005) 1635–1638. https://doi.org/10.1126/science.1110591.

[192] Y. Ringel, N. Maharshak, T. Ringel-Kulka, E.A. Wolber, R. Balfour Sartor, I.M. Carroll, High throughput sequencing reveals distinct microbial populations within the mucosal and luminal niches in healthy individuals, Gut Microbes. 6 (2015) 173–181. https://doi.org/10.1080/19490976.2015.1044711.

[193] Y. Uno, A. Munakata, Y. Ohtomo, Farewell to bacteremia caused by endoscopic injection - Effectiveness of a new injection catheter with a covered tip, Gastrointest. Endosc. 47 (1998) 523–525. https://doi.org/10.1016/S0016-5107(98)70255-X.

[194] A.G. Quintanilha, B. Zilberstein, M.A.A. Santos, D. Pajecki, E.G. Hourneaux Moura, P.R.A. Alves, F. Maluf-Filho, I. Cecconello, A novel sampling method for the investigation of gut microbiota, World J. Gastroenterol. 13 (2007) 3990–3995. https://doi.org/10.3748/wjg.v13.i29.3990.

[195] S.M. Huse, V.B. Young, H.G. Morrison, D.A. Antonopoulos, J. Kwon, S. Dalal, R. Arrieta, N.A. Hubert, L. Shen, J.H. Vineis, J.C. Koval, M.L. Sogin, E.B. Chang, L.E. Raffals, Comparison of brush and biopsy sampling methods of the ileal pouch for assessment of mucosa-associated microbiota of human subjects, Microbiome. 2 (2014) 5. https://doi.org/10.1186/2049-2618-2-5.

[196] E.R. Shanahan, L. Zhong, N.J. Talley, M. Morrison, G. Holtmann, Characterisation of the gastrointestinal mucosa-associated microbiota: a novel technique to prevent cross-contamination during endoscopic procedures, Aliment. Pharmacol. Ther. 43 (2016) 1186–1196. https://doi.org/10.1111/apt.13622.

[197] R.M. Shobar, S. Velineni, A. Keshavarzian, G. Swanson, M.T. DeMeo, J.E. Melson, J. Losurdo, P.A. Engen, Y. Sun, L. Koenig, E.A. Mutlu, The Effects of Bowel Preparation on Microbiota-Related Metrics Differ in Health and in Inflammatory Bowel Disease and for the Mucosal and Luminal Microbiota Compartments, Clin. Transl. Gastroenterol. 7 (2016) e143. https://doi.org/10.1038/ctg.2015.54.

[198] C. Tropini, E.L. Moss, B.D. Merrill, K.M. Ng, S.K. Higginbottom, E.P. Casavant, C.G. Gonzalez, B. Fremin, D.M. Bouley, J.E. Elias, A.S. Bhatt, K.C. Huang, J.L. Sonnenburg, Transient Osmotic Perturbation Causes Long-Term Alteration to the Gut Microbiota, Cell. 173 (2018) 1742-1754.e17. https://doi.org/10.1016/j.cell.2018.05.008.

[199] G. Jin, G. Wang, X. Liu, H. Cao, B. Wang, 977 – Intestine Microbiome Aspiration (IMBA)

Capsule: A New Autonomous and Minimally-Invasive Device for Whole Gut Microbiome Sampling and Mapping, Gastroenterology. 156 (2019) S-205. https://doi.org/10.1016/s0016-5085(19)37309-3.

[200] M. Rehan, I. Al-Bahadly, D.G. Thomas, E. Avci, Capsule robot for gut microbiota sampling using shape memory alloy spring, Int. J. Med. Robot. Comput. Assist. Surg. (2020). https://doi.org/10.1002/rcs.2140.

[201] H. Rezaei Nejad, B.C.M. Oliveira, A. Sadeqi, A. Dehkharghani, I. Kondova, J.A.M. Langermans, J.S. Guasto, S. Tzipori, G. Widmer, S.R. Sonkusale, Ingestible Osmotic Pill for In Vivo Sampling of Gut Microbiomes, Adv. Intell. Syst. 1 (2019) 1900053. https://doi.org/10.1002/aisy.201900053.

[202] J.F. Waimin, S. Nejati, H. Jiang, J. Qiu, J. Wang, M.S. Verma, R. Rahimi, Smart capsule for non-invasive sampling and studying of the gastrointestinal microbiome, RSC Adv. 10 (2020) 16313–16322. https://doi.org/10.1039/c9ra10986b.

[203] E.B. Hollister, C. Gao, J. Versalovic, Compositional and functional features of the gastrointestinal microbiome and their effects on human health, Gastroenterology. 146 (2014) 1449–1458. https://doi.org/10.1053/j.gastro.2014.01.052.

[204] F.C. Pereira, D. Berry, Microbial nutrient niches in the gut, Environ. Microbiol. 19 (2017) 1366–1378. https://doi.org/10.1111/1462-2920.13659.

[205] L. Barducci, J.C. Norton, S. Sarker, S. Mohammed, R. Jones, P. Valdastri, B.S. Terry, Fundamentals of the gut for capsule engineers, Prog. Biomed. Eng. 2 (2020) 042002. https://doi.org/10.1088/2516-1091/abab4c.

[206] N. Kurniawan, M. Keuchel, Technology, in: Video Capsul. Endosc., Springer Berlin Heidelberg, Berlin, Heidelberg, 2014: pp. 15–20. https://doi.org/10.1007/978-3-662-44062-9_3.

[207] M.E. McAlindon, F. Hagenmüller, D.E. Fleischer, Fields of Application, in: Video Capsul.

Endosc., Springer Berlin Heidelberg, Berlin, Heidelberg, 2014: pp. 5–13. https://doi.org/10.1007/978-3-662-44062-9_2.

[208] FDA Approval of Capsocam Plus, FDA Website. (2016). https://www.accessdata.fda.gov/cdrh_docs/pdf16/K161773.pdf (accessed January 9, 2019).

[209] Medtronic, Pillcam UGI - Capsule Specifications, Medtronic - Pillcam UGI Webpage. (n.d.). http://www.medtronic.com/covidien/en-us/products/capsule-endoscopy/pillcam-ugi-system.html (accessed February 27, 2018).

[210] Medtronic, Pillcam SB-3 - Capsule Specifications, Medtronic - Pillcam SB-3 Webpage. (n.d.). http://www.medtronic.com/covidien/en-us/products/capsule-endoscopy/pillcam-sb-3-system.html (accessed February 27, 2018).

[211] Olympus, EC-S10 - Capsule Specifications, Olympus Webpage. (n.d.). http://medical.olympusamerica.com/products/endocapsule-maj-2027 (accessed February 27, 2018).

[212] Capsovision, Capsocam Plus - Capsule Specifications, Capsovision Webpage. (n.d.). http://www.capsovision.com/physicians/product-specifications (accessed February 27, 2018).

[213] Aquilant Endoscopy, OMOM 2 - Capsule Specifications, Aqualiant Endosc. Webpage. (n.d.). http://www.aquilantendoscopy.com/products/products_detail.asp?subp=products_by_all.asp&idProduct=12874 (accessed February 27, 2018).

[214] L. Zhang, J. Shen, L. Guo, F. Cheng, Q. Fan, K. Ni, S. Xia, D. Zhou, Diagnostic value of OMOM capsule endoscopy for small bowel diseases in adults, Exp. Ther. Med. (2018). https://doi.org/10.3892/etm.2018.5864.

[215] M. Pioche, G. Vanbiervliet, P. Jacob, C. Duburque, R. Gincul, B. Filoche, J. Daudet, J.

Filippi, J.C. Saurin, Prospective randomized comparison between axial- and lateral-viewing capsule endoscopy systems in patients with obscure digestive bleeding, Endoscopy. 46 (2014) 479–484. https://doi.org/10.1055/s-0033-1358832.

[216] G.E. Tontini, F. Cavallaro, H. Neumann, L. Pastorelli, M.F. Neurath, L. Spina, M. Vecchi, Extensive small-bowel Crohn's disease detected by the newly introduced 360° panoramic viewing capsule endoscopy system, Endoscopy. 46 (2014). https://doi.org/10.1055/s-0034-1377358.

[217] Intromedic, Mirocam - Capsule Specifications, Intromedic Webpage. (n.d.). http://www.intromedic.com/eng/item/item_010100_view.asp?search_kind=&gotopage=1&no=3 (accessed February 27, 2018).

[218] SynMed, Mirocam - Capsule Specifications, SynMed Webpage. (n.d.). http://www.synmed.co.uk/products_capsule_endoscopy.htm (accessed February 27, 2018).

[219] F. Memon, G. Touma, J. Wang, S. Baltsavias, A. Moini, C. Chang, M.F. Rasmussen, A. Nikoozadeh, J.W. Choe, E. Olcott, R.B. Jeffrey, A. Arbabian, B.T. Khuri-Yakub, Capsule ultrasound device: Further developments, in: 2016 IEEE Int. Ultrason. Symp., IEEE, 2016: pp. 1–4. https://doi.org/10.1109/ULTSYM.2016.7728851.

[220] F. Memon, G. Touma, J. Wang, S. Baltsavias, A. Moini, C. Chang, M.F. Rasmussen, A. Nikoozadeh, Jung Woo Choe, A. Arbabian, R.B. Jeffrey, E. Olcott, B.T. Khuri-Yakub, Capsule ultrasound device, in: 2015 IEEE Int. Ultrason. Symp., IEEE, 2015: pp. 1–4. https://doi.org/10.1109/ULTSYM.2015.0168.

[221] N.J. Clear, A. Milton, M. Humphrey, B.T. Henry, M. Wulff, D.J. Nichols, R.J. Anziano, I. Wilding, Evaluation of the Intelisite capsule to deliver theophylline and frusemide tablets to the small intestine and colon, Eur. J. Pharm. Sci. 13 (2001) 375–384. https://doi.org/10.1016/S0928-0987(01)00134-8.

[222] C. Mc Caffrey, O. Chevalerias, C. O'Mathuna, K. Twomey, Swallowable-capsule technology, IEEE Pervasive Comput. 7 (2008) 23–29. https://doi.org/10.1109/MPRV.2008.17.

[223] M.A. Al-Rawhani, J. Beeley, D. Chitnis, S. Collins, D.R.S. Cumming, Wireless capsule for autofluorescence detection in biological systems, Sensors Actuators B Chem. 189 (2013) 203–207. https://doi.org/10.1016/j.snb.2013.03.037.

9. Tables

Table 1: Comparison of Capsule Endoscopes

Model	Length (mm)	Diameter (mm)	Imaging	Field of View	Direction	Frames per second	Battery Life (hrs)	Reference
Medtronic								
ESO2	26	11	CMOS	312^{O}	Front and Back Viewing	18	0.5	[206–208]
COLON2	32.3	11.6	CMOS	344^{O}	Front and Back Viewing	4-35	10	[206], [207]
UGI	32.3	11.6	CMOS	344^{O}	Front and Back Viewing	18-35	1.5	[209], [207]
SB	26	11	CMOS	140^{O}	Front Viewing	2	8	[210], [207]
SB-2	26	11	CMOS	156^{O}	Front Viewing	2	9	[210], [207]

SB-3	26.2	11.4	CMOS	156^{O}	Front Viewing	2-6	11-12	[210], [207]
Olympus								
EC1	26	11	CCD	145^{O}	Front Viewing	2	8	[211], [206]
EC1-S10	26	11	CCD	160^{O}	Front Viewing	2	12	[212], [206]
Aquilant Endoscopy								
OMOM 2	25.4	11		140^{O}	Front Viewing	2	6-8	[213], [214]
Capsovision								
Capsocam Plus	31	11	CMOS	360^{O}	Side Viewing	20	15	[208,212,215,216]
Intromedic								
MicroCam	24.5	10.8		170^{O}	Front Viewing	3	11-12	[217][218]

1

1 Table 2: Ultrasound Imaging Capsules

Capsule	Year First Published	Ultrasound Frequency	Field of View	Scanning Mechanism	Capsule Length (mm)	Capsule Diameter (mm)	Clinical Progress	Reference
Ultrasound Capsule (Stanford)	2015	5 MHz	360^{O}	Electronic	25 (proposed)	10 (proposed)	Benchtop Demonstration of Components	[20,219,220]
Ultrasound Capsule (MIT)	2014	30 MHz	360^{O}	Mechanical	40	10	*In Vivo* Animal Trials	[23][14]
Ultrasound Capsule (UK)	2019	30 MHz	N/A	None	30	10	*In Vivo* Animal Trials	[15]

Magnetically Driven Ultrasound Capsule (UK)	2019	30 MHz	N/A	None	39	21	*In Vivo* Animal Trials	[22]
Ultrasound Capsule (Shenzen)	2020	10 MHz	360^{O}	Mechanical	30	10	*In Vivo* Animal Trials	[21]

1

2 Table 3: Smart pills used in drug delivery and formulation studies (NS=Not Stated)

Capsule	Year First Published	Drug Delivery	Actuation Method	Capsule Length (mm)	Capsule Diameter (mm)	Payload Volume (ml)	Clinical Progress	Reference
Smith Kline French Cylinder	1961	Active	Electrothermal	16	8		*In Vivo* Animal Trials	[2].
HF-Capsule	1986	Passive	Thermomechanical	28	12	1	*In Vivo* Human Trials	[73–75]

InteliSite	1999	Passive	Thermomechanical	35	10	0.8	*In Vivo* Human Trials	[78,79,221]
Enterion	2000	Active	Thermomechanical	32	11	1	*In Vivo* Human Trials	[3,82][222]
Gröning Capsule (RF Signal)	2007	Active	Electrochemical	28	8.5	0.17	Benchtop Demonstration of Device	[81]
Intellicap	2013	Active	Electromechanical	27	11	0.3	*In Vivo* Human Trials	[46,85–87]
SmartTab	2021	Active	Smart Polymer	NS	NS	NS	*In Vivo* Animal Trials	[89]

1

2 Table 4: Smart pills used for the delivery of biologics

Capsule	Year First Published	Drug Delivery	Delivery Method	Capsule Length (mm)	Capsule Diameter (mm)	Reported Payload (mg)	Clinical Progress	Reference

Microneedle Capsule (MIT)	2015	Transepithelial	Epithelial Penetration (m)	20	10	N/A	*In Vivo* Animal Trials	[94]
LUMI Capsule	2019	Transepithelial	Epithelial Penetration (m)	30	9	0.3	*In Vivo* Animal Trials	[95]
Self Orientating Capsule	2019	Transepithelial	Epithelial Penetration (M)	NS	NS	0.3	*In Vivo* Animal Trials	[106]
RANI Therapeutics	2019	Transepithelial	Epithelial Penetration (m)	28	11	0.69 - 3.5	*In Vivo* Human Trials	[96][97]
Microneedle Capsule (DGIST)	2020	Transepithelial	Epithelial Penetration (m)	27	13	NS	*Ex Vivo* Animal Trials	[111]

	SonoCAIT	2021	Transepithelial	Epithelial Permeability (S)	30	11	External supply	*In Vivo* Animal Trials	[115]

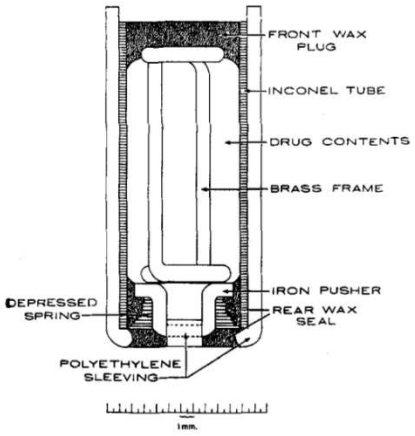
1

2

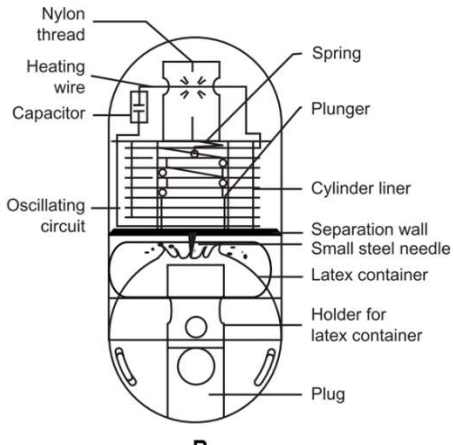
3

10. Figures

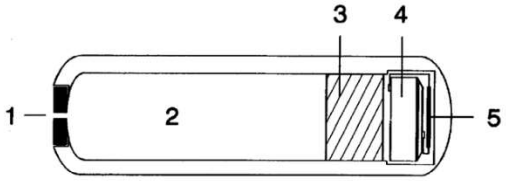
Figure 1: Diagnostic Capsules: A) PillCam Capsule Endoscope (Medtronic), B) SmartPill (Medtronic), C) Sonocap (Sonopill Project, Glasgow, UK) [15], D) Optical Coherence Tomography (OCT) pill (Harvard Medical School, USA) [17], E) Gas Sensing Capsule (Royal Melbourne Institute of Technology, Australia) [56], F) Autofluorescence Imaging Capsule (University of Glasgow, UK) [223], G) X-Ray Imaging Capsule (Check-Cap Ltd, Israel)[26], H) HemoPill Optical Blood Sensing Capsule (Ovesco Endoscopy AG, Germany)[52]



A

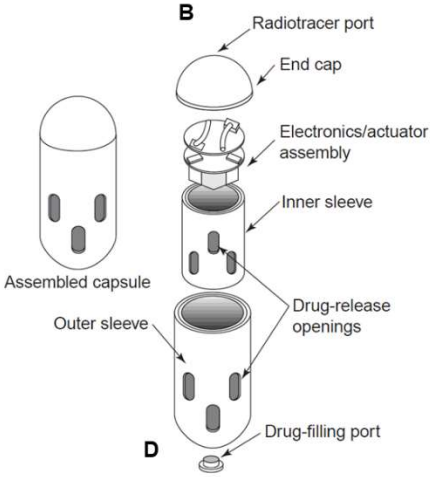


B

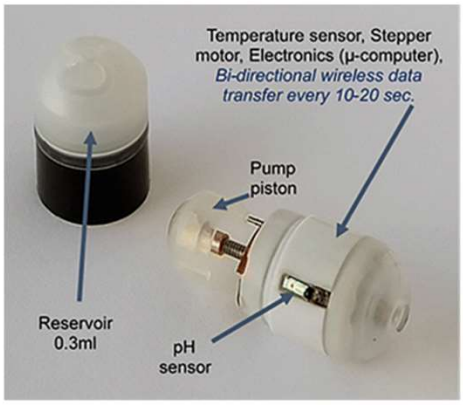


1: Release orifice
2: Drug reservoir
3: Piston
4: Gas-producing cell
5: Electronic circuit

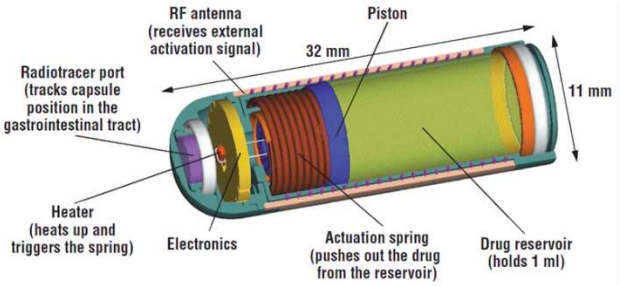
C



D



E



F

Figure 2: Smart pills for drug delivery and formulation. A) A 16mm x 8mm stainless steel cylinder sealed with wax that utilised inductive heating of the steel cylinder to melt the wax, releasing an internal spring that pushed the drug contents out and into the GI tract. Used in 1961 for drug absorption studies in canine models [2].B) The 28 mm x 12 mm HF- capsule utilised a 1 ml latex balloon as an internal drug reservoir made from a latex balloon that released the drug when punctured by a needle released when a nylon thread melted when trigged from an external signal [3], C) A capsule that emptied the drug reservoir due to the motion of a piston actuated by an electrolytic gas producing cell [72], D) The InteliSite drug delivery capsule that passive released the contents of the reservoir over time when an embedded shape memory alloy is heated due to an external trigger, causing the inner sleeve to rotate, aligning the drug release openings in the inner and outer sleeves [3], E) The 27 mm x 11 mm Intellicap drug delivery capsule contained a 0.3 ml internal drug reservoir, stepper motor and integrated pH sensor. The pH

sensor was used to determine the pill's location along the GI tract, and the stepper motor was used to actuate a piston that pushed out the reservoir contents. [88], F) The 34 mm long and 11 mm diameter Enterion capsule contained a 1ml internal drug reservoir, as well as a separate reservoir for a radioactive marker to enable tracking of the capsule by gamma scintigraphy. The drug reservoir is emptied when a small heater located behind a piston is powered by a coil within the capsule that is stimulated by induction. The heater breaks a polymer thread, releasing a coiled spring that forces the piston forward [222].

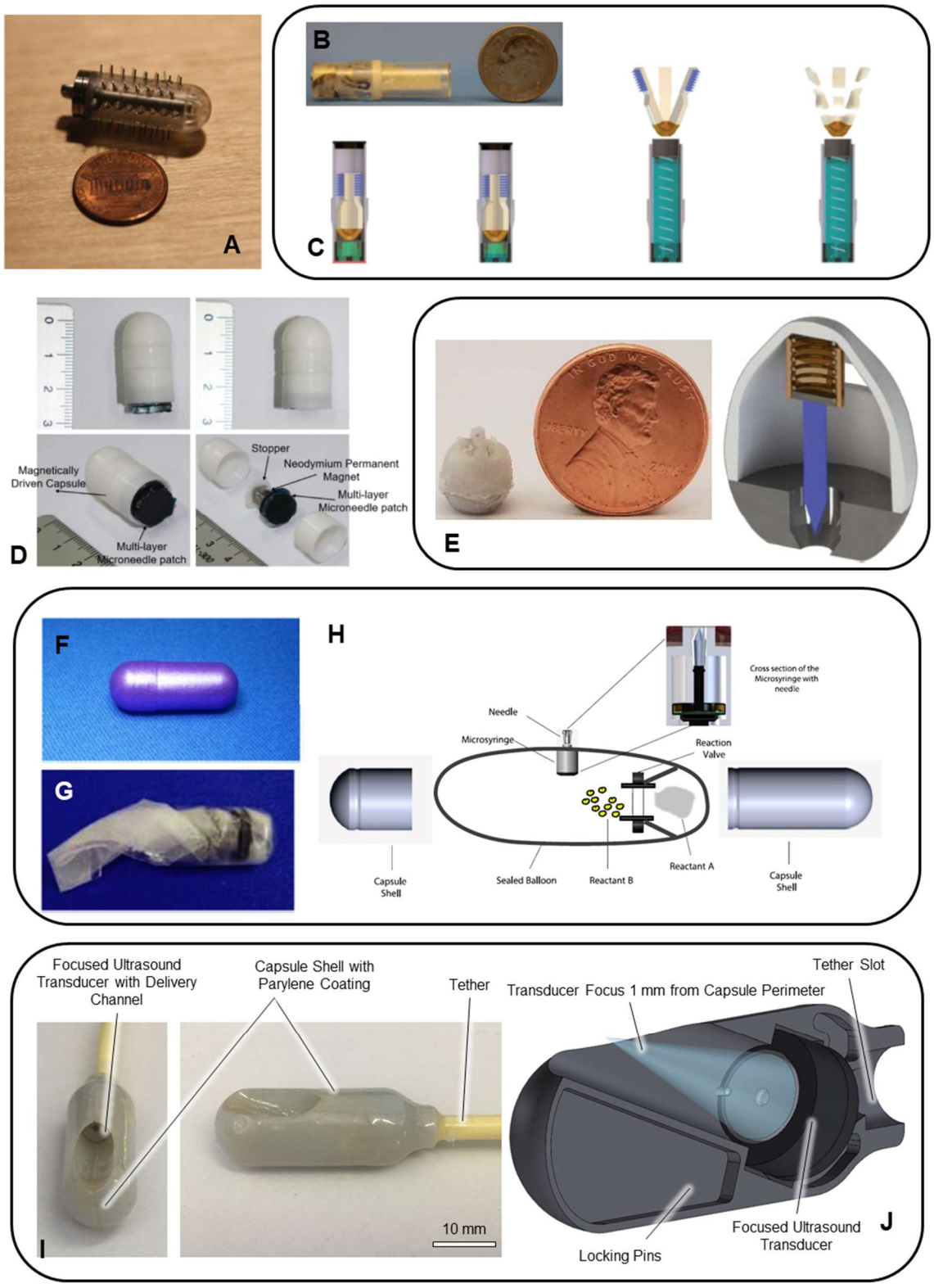


Figure 3: Drug Delivery Capsules for Biologics: A) MIT microneedle capsule [94], B) Side view of assembled and undeployed luminal unfolding microneedle injector (LUMI) capsule [95], C) Four stages of the LUMI actuation scheme, from left to right: i) enteric coating dissolves ii) water enters the bottom chamber, iii) the spring actuator dissolves, propelling device form the capsule iv) the drug is delivered, and the device dissolves [95], D) Magneticually actuated microneedle capsule from DGIST, South Korea [111], E) Self-orientating millimetre-scale applicator (SOMA) capsule shown to scale, along with cross-sectional view showing millimeter scale needle and spring for providing insertion force [106], F) A fully assembled, enteric coated RANI therapeutic capsule [97], G) A deflated, partially folded balloon contained within the Rani therapeutic capsule [96], H) [97], I) Annotated front and

side images of the SonoCAIT sonophoretic capsule [115], J) Annotated cross-sectional illustration showing the inside of the SonoCAIT capsule [115]

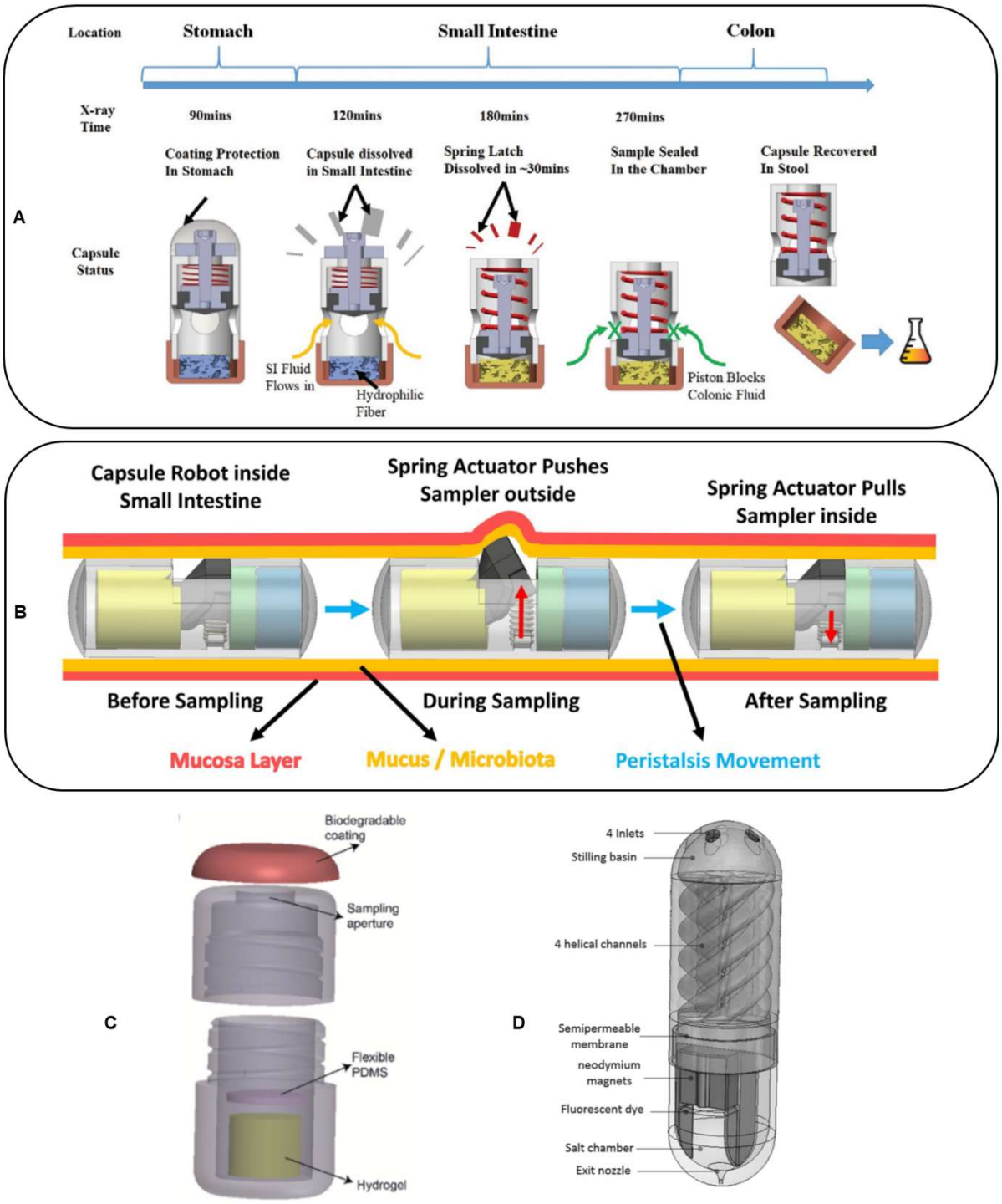


Figure 4: Microbiome Sampling Capsules. A) An enterically coated sampling capsule. The enteric coating dissolves in the small intestine, exposing a capsule compartment to luminal fluid. The compartment contains hydrophilic fibres that wick and capture the fluid. After some time, the luminal fluid dissolves a biodegradable spring, releasing a piston that seals the capsule, preventing further sampling. [199], B) A 30mm x 12mm 3D printed sampling capsule, which uses shape memory alloy springs to actuate the sampling mechanism that gently scapes the microbiota within the mucosa and stores it within a 500 µl sampling chamber. The shape memory alloy (Nitinol) spring is activated at 45°C by Joule heating induced by the onboard battery [200], C) A 9mm x 15mm sampling capsule consists of a 3D printed acrylic housing, a fast-absorbing hydrogel, and a flexible PDMS membrane. Fluids containing samples of the GI microbiota enter the device through a sampling aperture on the device's cap. The hydrogel swells due to fluid absorption, protecting the samples and pushing the flexible PDMS membrane to

prevent further fluid exchange. The hydrogel encapsulated sample can be retrieved due to the screw cap design [202], D) Osmotic microbiome sampling pill is primed by injecting water into the salt chamber and the helical channels. The capsule is enterically coated before ingestion to protect it from the stomach. The integrated magnets allow the capsule to be held in a specific part of the GI tract. Osmotic pressure induced flow occurs along the helical channels through the semipermeable membrane, drawing microbiota in. [201]