

# Smart pills for gastrointestinal diagnostics and therapy

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1 **Smart pills for gastrointestinal diagnostics and therapy**

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

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

## 9 **1. Introduction**

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

21 Though smart pills capable of gastric pH monitoring were first reported as far back as 1965  
22 [1] and simple devices and smart pills for drug absorption studies along the GI tract were  
23 reported in 1961 and 1982, respectively [2] [3], it is arguably the introduction of the capsule  
24 endoscope (CE) in 2000 [4,5] that has led to the increase in the number of smart pills reported  
25 in recent years [6]. The CE enabled inspection of the small bowel, which was not easily  
26 accessible by conventional endoscopy. However, CE remains the most widely used smart pill

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

## 16 **2. Smart Pills for Diagnosis**

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

### 24 **2.1. Imaging**

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

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

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

19 Autofluorescence imaging illuminates tissue with short wavelengths of light (380-500 nm) to  
20 excite endogenous or exogenous fluorophores; absorption of the incident light by the  
21 fluorophores causes them to emit light at longer wavelengths (490-590 nm). This principle  
22 allows the differentiation between malignant and benign tissue to occur easily due to reduced  
23 emission from malignant tissue [19]. This imaging technology has been widely used with  
24 conventional endoscopy. However, only one group has sufficiently miniaturised the technology  
25 to fit within a smart pill due to the use of single-photon avalanche diode (SPAD) imaging  
26 arrays, capable of detecting a single photon of light, giving a sensitivity of 19 pW/cm<sup>2</sup> using a  
27 10 ms exposure time that is capable of measuring 20 μM of exogenous fluorophores such as

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

6 Endoscopic ultrasonography is also clinically accepted and in routine clinical use. The  
7 miniaturisation of this technology to fit within a capsule has been a goal of several groups.  
8 Though this technology is still in its infancy, several smart pills capable of ultrasound imaging  
9 have been reported based on different technological approaches [14,15,20,21], which are  
10 summarised in Table 2. The Khuri-Yakub group at Stanford University, USA, are attempting  
11 to produce an ultrasound imaging capsule incorporating a multi-element ring array to generate  
12 a 360° image of the intestinal wall [20]. This technology employs an ultrasound frequency of  
13 5 MHz, which would be most suitable for imaging the organs located beyond the GI tract due  
14 to the greater penetration depth and lower spatial resolution achievable at those frequencies.  
15 This technology has yet to be integrated into a capsule or tested *in-vivo*. The UK's Sonopill  
16 project focused on single-element transducers operating at frequencies as high as 30 MHz.  
17 This high-resolution ultrasound sacrifices penetration depth for greater spatial resolution  
18 capable of imaging subsurface features such as structural and tissue composition. However,  
19 it should be noted that the penetration is sufficient to enable the imaging of the intestinal wall  
20 at a resolution sufficient to distinguish each of the tissue layers in the small bowel. This  
21 transducer was used in the production of a tethered ultrasound imaging smart pill that was  
22 shown to be capable of acquiring detailed images of a porcine small bowel during *in-vivo* tests  
23 [15]. This work was subsequently used to develop a magnetically actuated capsule capable  
24 of optical and ultrasound imaging [22]. However, the capsule could not image the small bowel  
25 radially in both cases. Subsequent ultrasound imaging capsules developed by Qiu [21] and  
26 Lee [23] achieved radial imaging of the wall of the small intestine through mechanical rotation  
27 of 30 MHz and 10 MHz transducers, respectively. The resolution of the Qiu capsule, which

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

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

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

9 Optical coherence tomography is a sub-mucosal imaging technique capable of high spatial  
10 resolution comparable to conventional histological analysis of excised biopsy tissue (10 µm  
11 axial and 30 µm lateral resolution). It operates by measuring the time delay and intensity of  
12 backscattered or back-reflected light from an optical beam scanned across the sample surface  
13 [29]. High sensitivity (90.0%) and specificity (83.3%), sufficient to differentiate between  
14 Crohn's disease and ulcerative colitis, have been achieved with colonoscopically delivered  
15 OCT, demonstrating its potential for the diagnosis of inflammatory bowel disease [30].  
16 Attempts to integrate OCT into smart pills resulted in two tethered devices primarily  
17 demonstrated in the oesophagus [17,18]. Both pills rely on an external light source that  
18 transmits light to optics integrated within the pill via an optical fibre within the tether and  
19 mechanical scanning to generate the image. The tethered capsule developed by Gora et al.  
20 was 12.8 mm in diameter and 24.8 mm long with side-viewing OCT capable of generating  
21 radial images at 20 frames per second with 30 µm lateral and 7 µm axial resolution in humans  
22 [17]. Though manual pullback of the device facilitates rapid imaging for screening purposes,  
23 it may not be sufficient to provide the stability or repeatability needed for volumetric OCT [18].  
24 The 12 mm diameter and ~35 mm long device, produced by Liang et al. [18], were shown to  
25 generate volumetric OCT in porcine models. The ability to achieve volumetric OCT was due  
26 to an integrated longitudinal scanning system that could track non-uniformities along the scan  
27 trajectory, enabling compensation in post-processing. However, the tether used made the



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

## 4 **2.2. Physical Sensing**

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

### 9 **2.2.1. Pressure Sensing**

10 Changes in the GI system's physical parameters may indicate a pathological condition. This  
11 is especially true for bowel motility changes, which are associated with 40% of GI conditions  
12 resulting in abdominal discomfort, pain and altered bowel habits [31,32]. Current methods of  
13 assessing bowel motility can include the endoscopic insertion of manometers, which can be  
14 uncomfortable for patients and precludes investigation of the small intestine. These limitations  
15 have led to the development of several smart pills capable of measuring pressure [33–36].  
16 Since 2006, the SmartPill is the only wireless CE device with pressure-sensing capabilities  
17 currently on the market with FDA approval [33]. SmartPill contains a temperature sensor (25–  
18 49°C), a pH sensor (pH 0.05-9.0), a single pressure sensor with an operating range 0–46 kPa  
19 and a sensitivity of  $\pm 0.650$  kPa that can record the pressure of its environment. This capsule  
20 is primarily used in motility studies to measure the transit time between different regions of the  
21 GI tract based on changes in pH and pressure.

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

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

#### 4 **2.2.2. Temperature Sensing**

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

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

#### 18 **2.2.3. pH Sensing**

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

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

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

12

### 13 **2.3. Chemical and Biological Sensing**

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

#### 20 **2.3.1. Haemoglobin and other Soluble Biomarkers**

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

1 Conventional WLI CE can be used to identify blood in the stomach, but it cannot easily  
2 differentiate between past and active GI bleeding in the stomach. Qiao demonstrated a  
3 colourimetric detection pill that used a hue–saturation light colour detection method on blood  
4 cells selectively channelled into a measurement chamber [49]. This chamber included white  
5 LEDs for illumination, a colour sensor and an adsorptive colour-sensitive film that undergoes  
6 a change from white to red in the presence of haemoglobin. *In vitro* trials with different blood  
7 concentrations showed that the system could measure haemoglobin concentrations as low as  
8 2.375 mg per ml, which is reported to be less than that found in areas of GI bleeding. Nemiroski  
9 also developed a smart pill to detect GI bleeding [48]. Similar to an earlier *in vivo*  
10 demonstration by members of that group [51], the Nemiroski wireless, battery-powered pill  
11 detects active bleeding through the intravenous injection of fluorescein, a FDA compliant  
12 fluorescent contrast agent whose spectra (absorption peak at 494 nm, emission peak at 512  
13 nm) does not overlap with that of gastric juices (absorption peak at 288 nm; emission peak at  
14 350 nm). Fluorescein emits light in the presence of blood, acting as a proxy biomarker for the  
15 detection of active bleeding in the stomach. Benchtop tests have demonstrated that the  
16 system can detect concentrations of fluorescein as low as 20 nM. However, the system's  
17 performance varies with the pH of the stomach as the spectral properties and quantum yield  
18 of fluorescein shift with pH, which can be problematic after the patient ingests water. No further  
19 work has been published on this pill.

20 Another pill developed to detect active bleeding is the commercially available HemoPill [50]  
21 (OVESCO, Tuebingen, Germany). This battery-powered pill of length 26.3 mm and diameter  
22 7 mm, contains an optical sensor to measure the optical absorption at 415 nm between an  
23 LED and a photodetector placed within a recessed channel on the pill's surface [52]. At this  
24 wavelength, optical transmission through blood is at a minimum and is three orders of  
25 magnitude less than transmission at a reference wavelength (720 nm). The optical sensor can  
26 detect haemoglobin by measuring the relative change in absorption at 415 nm to the reference  
27 signal at 720 nm. Preliminary *in vivo* tests using human volunteers have been conducted [53].

1 Initial tests were performed on a healthy volunteer with simulated GI bleeding under various  
2 conditions through periodic ingestion of 20 ml blood. The results were compared with baseline  
3 readings from the same volunteer under the same conditions without blood intake. The  
4 capsule successfully detected simulated GI bleeding after each ingestion of blood, with the  
5 detection algorithm showing a correlation ( $R^2 = 0.9016$ ) between changing sensor signal within  
6 10 min of capsule ingestion and increased gastric blood concentration.

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

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

### 16 **2.3.2. Gaseous Biomarkers**

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

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

### 6 **2.3.3. Biological Sensing**

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

## 15 **3. Future Directions of Diagnostic Smart Pills**

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

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

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

#### 12 **4. Smart Pills for Therapy**

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

##### 17 **4.1. Drug Delivery and Drug Formulation**

18 The use of smart pills for aiding the formulation of pharmaceutical agents or their delivery to  
19 the site of GI pathology has been the subject of much research. To date, most of these pills  
20 have been for the delivery or assessing the formulation of small-molecule drugs. The  
21 specifications of several of these pills have been summarised for ease of comparison in Table  
22 3.

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

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

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

#### 20 **4.1.1. Passive Drug Delivery**

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

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



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

5 Another smart pill also used for the study of pharmacokinetics is the IntelliSite Companion  
6 Capsule (Innovative Devices, Raleigh, NC, USA), which is shown in Figure 2D, that was  
7 developed due to challenges regarding the usage of the earlier HF capsule outside of Europe  
8 and to be used in conjunction with gamma scintigraphy [78]. An earlier version of the IntelliSite  
9 device consisted of a 10 mm x 35 mm plastic capsule contains and 0.8 ml internal drug  
10 reservoir. The capsule contents are released when externally triggered by an RF signal, which  
11 causes integrated resistors to begin to heat up. The thermal energy is dissipated to shape  
12 memory alloy metal wires that straighten up at 40°C, generating a mechanical force. This  
13 force causes the inner sleeve of the capsule to rotate, aligning ports located on the inner and  
14 outer sleeves and releasing the drug via diffusion. Later IntelliSite devices changed the mode  
15 of operation [79]; the capsule contained an outer sleeve and inner sleeve. The inner sleeve  
16 was removable and mounted on a spring. The inner sleeve was held in place by a cap kept in  
17 place by shape memory alloy wires. The heating of these wires was again triggered by an  
18 external RF source, causing the cap to be released and the inner cage-like sleeve containing  
19 the drug to be released. However, the IntelliSite capsule was known for being susceptible to  
20 gradual, preactivation leakage of liquid formulations due to a poor seal between the inner and  
21 outer sleeves and the energy required to heat the shape memory alloy wires resulted in  
22 activation times of 2 minutes or greater depending on the depth of the capsule within the body  
23 [77].

#### 24 **4.1.2. Active Drug Delivery**

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

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

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

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

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

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

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

#### 18 **4.2. Drug Delivery Capsules for Biologics**

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

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

### 3 **4.2.1. Epithelial Penetration**

4 The only method being investigated for the delivery of biologics via epithelial penetration is  
5 through the use of microneedles. While transdermal drug delivery has been the focus of most  
6 research to date concerning the use of microneedles [92,93], there have been some  
7 investigations on their use for oral drug delivery [94–97]. Various materials, such as metal  
8 [94], sugars [98] and polymers [95] have been investigated. Epithelial penetration using  
9 microneedles is an attractive solution due to the fact that studies of GI injection for therapeutic  
10 delivery have shown a quicker pharmacokinetic response compared to subcutaneous injection  
11 [94]. The time to hypoglycaemic onset, defined as a drop in the initial blood-glucose  $\geq 5\%$ ,  
12 when 10 units of rapid-acting insulin in 1 ml of 0.9% saline were administered using a 25G  
13 needle in 75-80 kg Yorkshire pigs were measured to be  $23.08 \pm 7.00$ ,  $6.28 \pm 4.48$ ,  $6.66 \pm 1.65$ ,  
14 and  $16.91 \pm 6.39$  min for subcutaneous, gastric, duodenal, and colonic administration,  
15 respectively [94]. Another advantage of epithelial penetration via microneedles is the lack of  
16 sharp pain receptors along the intestine, enabling painless delivery of therapeutics.

17 With regards to safety, the height of microneedles rarely exceeds 0.2 cm [99], which is less  
18 than the 3-16 cm size range of ingested objects requiring surgical removal due to the risk to  
19 the individual's health [100]. Additionally, the administration of drugs in the GI tract via injection  
20 is a routine part of many treatments for conditions such as bleeding ulcers and polypectomy  
21 [101–103]. However, few studies have been performed on the effect of repeated or prolonged  
22 usage of microneedles on the GI tract. Studies performed with transdermal microneedles  
23 suggest that some microneedles may induce temporary and minimal inflammation around the  
24 insertion site [104]; similar studies have yet to be performed on the intestinal epithelium to  
25 determine whether a similar response is observed. While microneedles are a relatively safe  
26 way of penetrating the epithelium than other alternatives, further studies would be welcome to  
27 clarify the optimal and safest way of using this technology.

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

12 The Langer Group demonstrated that capsule-based microneedle devices could be ingested  
13 and excreted without perforating the intestine or retention using a capsule that is 20 mm in  
14 length and 10 mm in diameter with an unknown number of 25G hollow needles arranged in a  
15 radial pattern protruding 5 mm from the capsule surface, this capsule is shown in Figure 3A  
16 [94]. However, this design is limited in that penetration of the mucosa and the subsequent  
17 release of insulin is reliant on the peristaltic compression of this capsule by the small intestine.  
18 The pressure exerted by the surrounding tissue on the capsule will vary from patient to patient  
19 [105]. Additionally, the presence of chyme will also affect the microneedle penetration. This  
20 potential variability in the number of microneedles penetrating the mucosa and the depth of  
21 penetration from pill to pill will affect dosage reliability.

22 Later polymer microneedle based devices developed by the same group have overcome this  
23 limitation by developing devices that exert a mechanical force against the intestinal mucosa  
24 [95]. The device, shown in Figure 3B and C, consisted of an outer cylindrical tube of 30 mm  
25 length and 9 mm diameter that was coated in a poly (methacrylic acid co-ethyl acrylate)  
26 coating that dissolved at a pH of  $\geq 5.5$ . The inside of the tube contained a compressed steel  
27 spring encapsulated in a polyethylene glycol (PEG) coating (molecular weight: 3,500), which,

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

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

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

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

5 While the intestines are insensate to sharp sensations, they can detect distension and stretch.  
6 Tolerability studies with human volunteers of the RANI therapeutic capsule with balloons  
7 ranging in diameter from 21 mm to 25 mm demonstrated an absence of pain or discomfort  
8 when the balloons deployed, suggesting the forces generated were insufficient to activate  
9 intestinal stretch receptors. Safety studies of the capsule were only concerned with the  
10 excretion of the entire device, which was achieved. No histological examination of the tissue  
11 surrounding the needle injection site was reported in either study [96,97]. The capsule was  
12 reported to reliably deliver the drugs 80% of the time with the 25 mm diameter balloon after  
13 ingestion; reduced reliability was achieved with the smaller balloons. The bioavailability of  
14 octreotide delivered using this capsule was 65%, greater than the  $\leq 1\%$  obtained previously  
15 [109]. Pharmacokinetic data using the capsule is comparable to delivery via parenteral routes.  
16 However, the mass of drug that can be delivered with this technology is limited to 3.5 mg by  
17 the size of the needle. Additionally, the variability of GI transit times from person to person  
18 may preclude the use of this technology for time-sensitive therapeutics such as insulin, where  
19 predictability is crucial.

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

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

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

#### 10 **4.2.2. Epithelial Permeability**

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

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

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



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

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

21 Miniaturised ultrasound transducers were integrated into a capsule format by Stewart et. al to  
22 assess the feasibility of *in vivo* ultrasound-mediated drug delivery trials in the porcine small  
23 bowel via smart pill [115]. An 11 mm diameter, 30 mm long tethered capsule, shown in Figure  
24 3I and J, contained an integrated focused ultrasound transducer that emitted a 3.98 MHz  
25 signal and was inserted into the small bowel via a surgical stoma. This frequency was chosen  
26 based on earlier *in vitro* tests using Caco-2 monolayers [116,117]. The capsule delivered a  
27 solution consisting of fluorescent quantum dots and microbubbles into the small bowel through

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

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

#### 24 **4.3. Drug Adherence Monitoring**

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

1 124]. Despite the World Health Organisation (WHO) recognising the significant impact of  
2 greater medication adherence on public health compared to any improvement in a specific  
3 medical treatment [125], the ability to identify nonadherence by clinicians is limited [121]; its  
4 causes are complex [126] and attempts to improve adherence have either been mixed,  
5 complex or costly [127].

6 This challenging problem has spurred the development of several technological solutions  
7 [128,129], some of which take the form of an ingestible pill [130,131]. Two smart pills were  
8 commercialised and approved by regulatory authorities, the pill from Proteus Digital Health  
9 approved by the FDA in 2012 [132] and the Etect-Rx pill, also known as the ID-Cap pill, which  
10 the FDA approved in 2019. Proteus Digital Health subsequently closed in 2019, but their  
11 technology continues to be used in the Abilify MyCite system sold by Otsuka Pharmaceutical  
12 to monitor ingestion of aripiprazole [133].

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

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

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

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

#### 7 **4.4. Non-Pharmacological Therapeutic Smart Pills**

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

##### 15 **4.4.1. Obesity**

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

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

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

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

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

#### 6 **4.4.2. Constipation**

7 Constipation is a common disorder that is, in most cases, related to some dysfunction of the  
8 GI tract. There is a need for innovative solutions to this condition due to the high-cost burden  
9 on healthcare systems linked to chronic constipation [157], the high prevalence of the  
10 condition [158], poor quality of life [159] and low patient satisfaction with current treatments  
11 [160]. One proposed solution is the VIBRANT capsule (Vibrant Ltd. Yokneam, Israel), which  
12 is a 24 x 11 mm vibrating ingestible capsule [161–163]. This battery-powered capsule consists  
13 of two segments that are attached together but free to move independently. The actuation of  
14 the two segments is achieved by an internal ferromagnetic shaft connected to a solenoid and  
15 springs. External control of the current flowing through the solenoid enables the frequency,  
16 magnitude and duration of vibrations within the colon to be adjusted. Initial *in vivo* trials with  
17 26 human adult patients reported an increase of spontaneous bowel movements (SBMs) in  
18 23 patients, with the mean number of SBMs/week increasing from  $2.19 \pm 0.67$  to  $3.79 \pm 1.31$ .  
19 However, 12 members of the study reported adverse effects potentially related to the study,  
20 such as abdominal pain, diarrhoea, flatulence and gastroenteritis [161]. However, subsequent  
21 *in vivo* human studies showed no significant difference in the number of SBMs between those  
22 given the VIBRANT capsule and those given a sham capsule [162,163] though no significant  
23 adverse effects were reported that were related to the VIBRANT capsule. Further optimisation  
24 of the vibration parameters of the capsule have been repeatedly proposed as a means of  
25 increasing device efficacy.

#### 26 **4.4.3. Electrical Stimulation**

1 Multiple studies have demonstrated that electrical stimulation can modulate GI motility and,  
2 therefore, may be a promising alternative to pharmacological treatments of GI dysmotility  
3 [164]. Implantable electrical stimulation devices for treating gastroparesis [165] and obesity  
4 [166] are in clinical use. A proof of concept, ingestible device was recently demonstrated to  
5 induce muscle contraction within the stomach through electrical stimulation [167]. The device  
6 was based on an earlier self-orientating capsule design [106], with the stainless steel needle  
7 of that device connected to an external microcontroller and silver oxide battery via flexible  
8 stranded core wires. These external electrical components were encapsulated in a layer of  
9 PDMS to protect them from the gastric acid, and a thin layer of Parylene C was deposited onto  
10 the shaft of the needle to target electrical current flow into the lower muscular layer of the  
11 stomach tissue via the uncoated, conductive needle tips. The self-orientating nature and the  
12 effect of gravity led the device to settle in the stomach location near to where gastric  
13 pacemakers are typically placed. The microcontroller was used to mimic the pulses created  
14 by a FDA-authorised gastric electrical stimulation system by generating two consecutive  
15 voltage pulses of length 330  $\mu\text{s}$  with a 70 ms gap in between. These pulses were repeated  
16 every 5 seconds. The voltage pulse amplitude within the stomach was measured to range  
17 between 0.31 to 0.42 V, and was intended to generate a charge density at the electrode-tissue  
18 interface of 2.2  $\mu\text{C}\cdot\text{cm}^{-2}$ . Three devices were tested in adult porcine animal models and  
19 muscular stimulation was observed via ultrasound imaging. As recognised by the authors,  
20 future devices should use needles made from platinum or iridium to avoid corrosion and use  
21 a current-controlled system to mitigate the effects of changing electrical impedance on  
22 stimulation due to tissue fibrosis. The device only remains attached to the stomach in the  
23 absence of digestion, limiting the use of this technology to applications where short term or  
24 repeated interventions are required. This will also require further studies to assess this  
25 technology's efficacy in humans with gastroparesis.

## 26 **5. Future Directions for Therapeutic Smart Pills**



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

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

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

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

3 Another challenge, specific to smart pills that deliver pharmacological therapeutics, is the  
4 onboard storage volume. Most smart pills developed to date have storage volumes between  
5 0.3 to 1 ml due to onboard electronics, telemetry, batteries, actuators, sensors, and other  
6 components that take up space. As these devices become more sophisticated due to  
7 increased electronic and mechanical integration, there will be implications for dosages  
8 achievable with these pills. This factor may necessitate greater pharmaceutical potency or  
9 increased reliance on miniaturisation technology such as microelectromechanical systems or  
10 microfluidics to reduce the size of mechanical components. Integration of these systems within  
11 the pill also has economic implications for this technology due to the associated increase in  
12 cost. This may make it prohibitive to use this technology to treat many conditions until  
13 advantages of scale enable greater usage. Another factor to consider is the sustainability of  
14 this technology due to the nature of these pills being single-use and their removal of the body  
15 via excretion. If the technology comes into wider use, then there may be environmental  
16 challenges to consider due to increased electronic waste. This may be avoided by a shift  
17 towards biodegradable materials, though the use of such materials in creating electronic  
18 components is still in its infancy [174].

## 19 **6. Smart Pills for Biopsy and Sampling.**

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

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

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

### 11 **6.1. Tissue Biopsy**

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

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

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

### 3 **6.2. Microbiome Sampling**

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

13 Several pills, some of which are shown in Figure 4, have been demonstrated that sample the  
14 GI microbiome [199–202]. These capsules use various sampling methods such as springs  
15 and wicking materials [199], shape memory alloys [200], osmotic pumps [201], biodegradable  
16 coatings [202]. Most of these pills sampled along the entire length of the GI tract and have not  
17 demonstrated sampling within specific regions of the GI tract. Information on whether they can  
18 be used to determine the spatial distribution of the microbiome along the GI tract, which would  
19 be advantageous over widely used faecal proxies, does not exist. One pill, shown in Figure  
20 4B, was designed to sample the microbiome within the mucus layer and reseal after capture,  
21 though *in vivo* tests have yet to be conducted [200]. The rest of the pills reported to date, such  
22 as those in Figure 4A and C, sample the microbiota of the luminal fluid and not that of the  
23 mucus. Where sampling occurs and what is sampled has implications for the quality of the  
24 information derived from such devices. This is because the composition and diversity of the  
25 microbiome varies longitudinally along the GI tract and axially, from the lumen to the mucosal  
26 surface [203,204].

## 1    **7. Future Directions of Smart Pills**

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

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1 **9. Tables**

2 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°	Front and Back Viewing	18	0.5	[206–208]
COLON2	32.3	11.6	CMOS	344°	Front and Back Viewing	4-35	10	[206], [207]
UGI	32.3	11.6	CMOS	344°	Front and Back Viewing	18-35	1.5	[209], [207]
SB	26	11	CMOS	140°	Front Viewing	2	8	[210], [207]
SB-2	26	11	CMOS	156°	Front Viewing	2	9	[210], [207]



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

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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°	Electronic	25 (proposed)	10 (proposed)	Benchtop Demonstration of Components	[20,219,220]
Ultrasound Capsule (MIT)	2014	30 MHz	360°	Mechanical	40	10	<i>In Vivo</i> Animal Trials	[23][14]
Ultrasound Capsule (UK)	2019	30 MHz	N/A	None	30	10	<i>In Vivo</i> Animal Trials	[15]

Magnetically Driven Ultrasound Capsule (UK)	2019	30 MHz	N/A	None	39	21	<i>In Vivo</i> Animal Trials	[22]
Ultrasound Capsule (Shenzen)	2020	10 MHz	360°	Mechanical	30	10	<i>In Vivo</i> Animal Trials	[21]

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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		<i>In Vivo</i> Animal Trials	[2].
HF-Capsule	1986	Passive	Thermomechanical	28	12	1	<i>In Vivo</i> Human Trials	[73–75]

InteliSite	1999	Passive	Thermomechanical	35	10	0.8	<i>In Vivo</i> Human Trials	[78,79,221]
Enterion	2000	Active	Thermomechanical	32	11	1	<i>In Vivo</i> 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	<i>In Vivo</i> Human Trials	[46,85–87]
SmartTab	2021	Active	Smart Polymer	NS	NS	NS	<i>In Vivo</i> Animal Trials	[89]

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

SonoCAIT	2021	Transepithelial	Epithelial Permeability (S)	30	11	External supply	<i>In Vivo</i> Animal Trials	[115]
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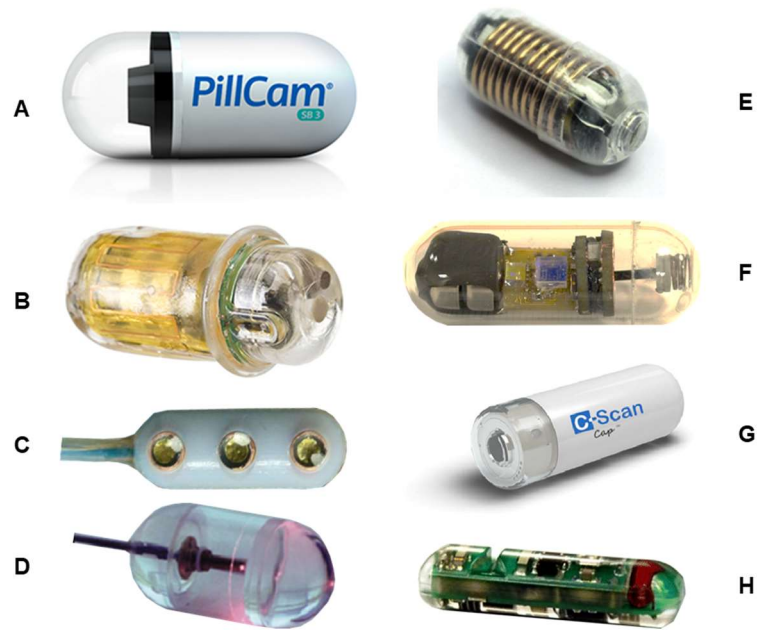
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## 1 10. Figures

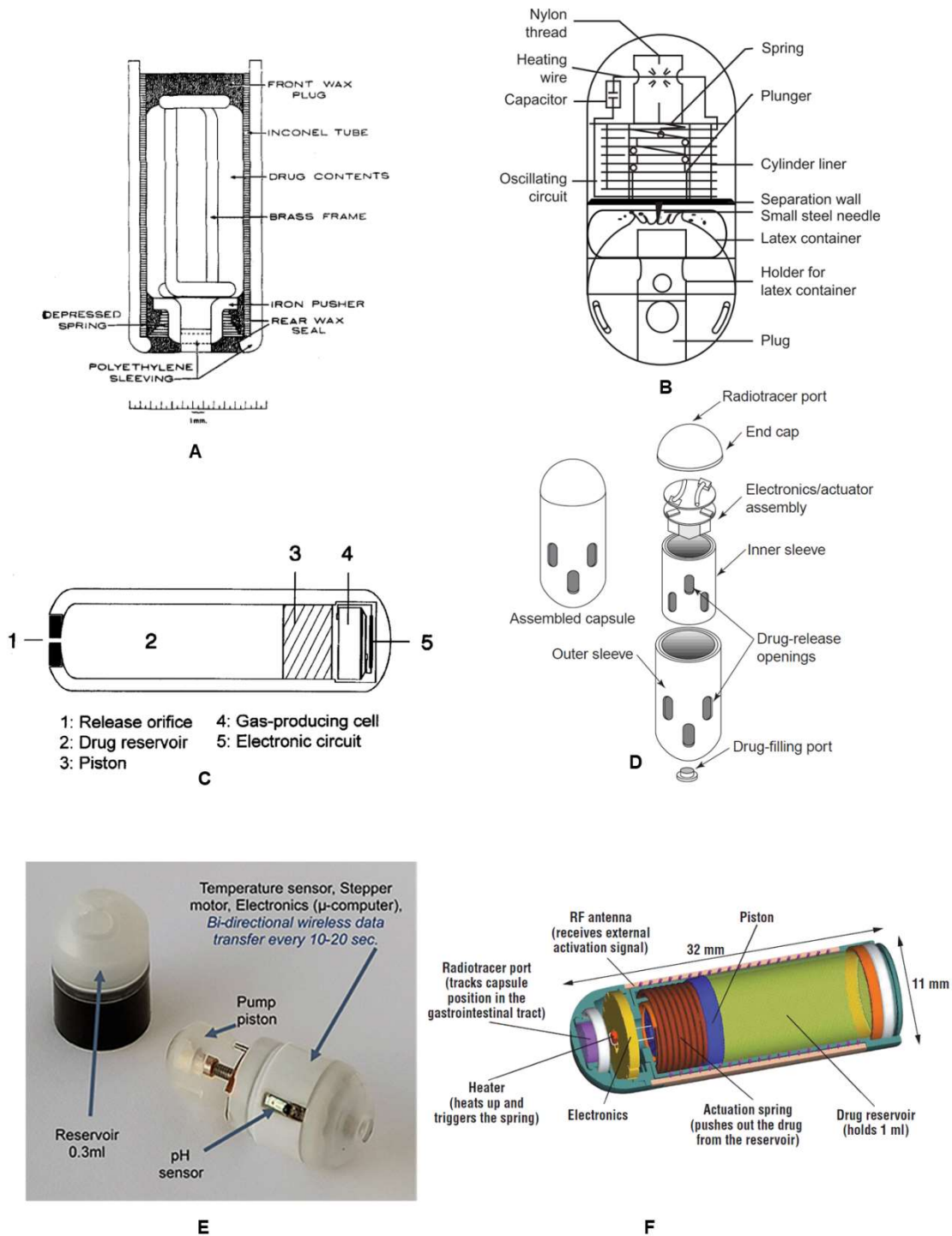
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3 Figure 1: Diagnostic Capsules: A) PillCam Capsule Endoscope (Medtronic), B) SmartPill (Medtronic), C)  
4 Sonocap (Sonopill Project, Glasgow, UK) [15], D) Optical Coherence Tomography (OCT) pill (Harvard Medical  
5 School, USA) [17], E) Gas Sensing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

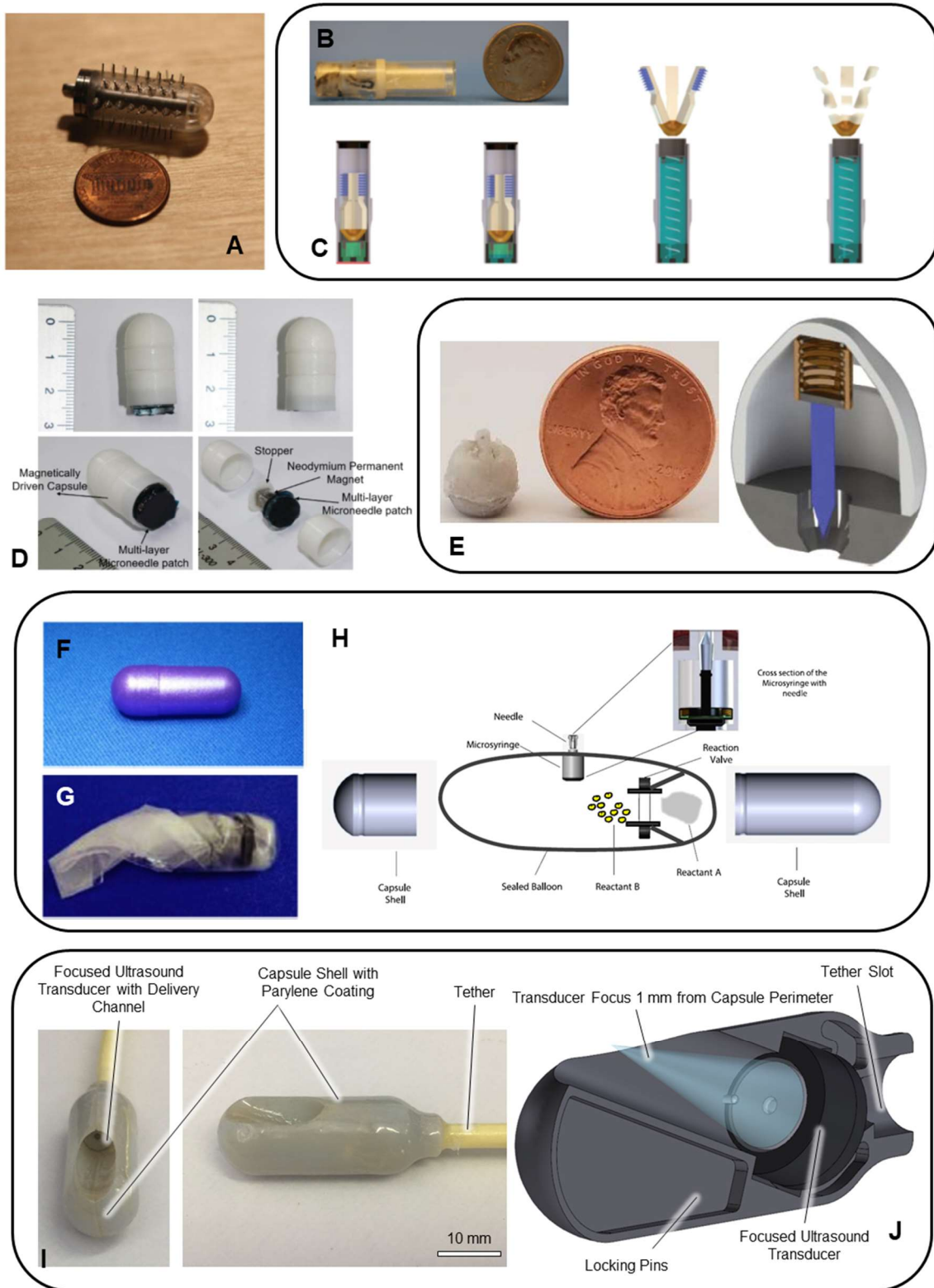




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Figure 2: Smart pills for drug delivery and formulation. A) A 16mm x 8mm stainless steel cylinder sealed with wax that utilised inductive heating of the steel cylinder to melt the wax, releasing an internal spring that pushed the drug contents out 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 triggered 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 IntelliSite drug delivery capsule that passively 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

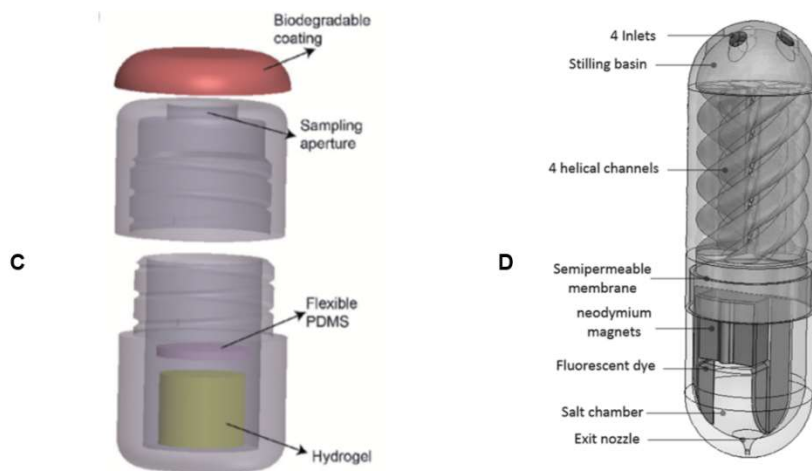
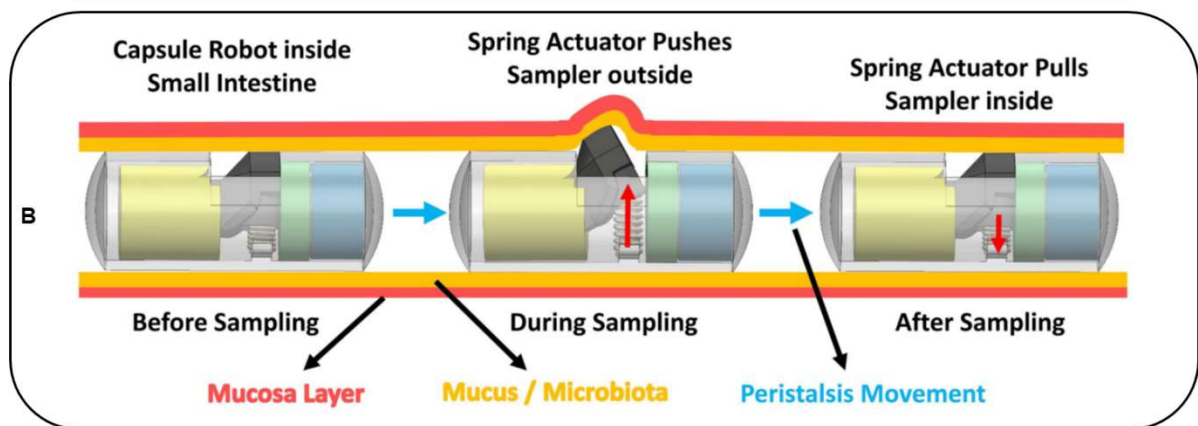
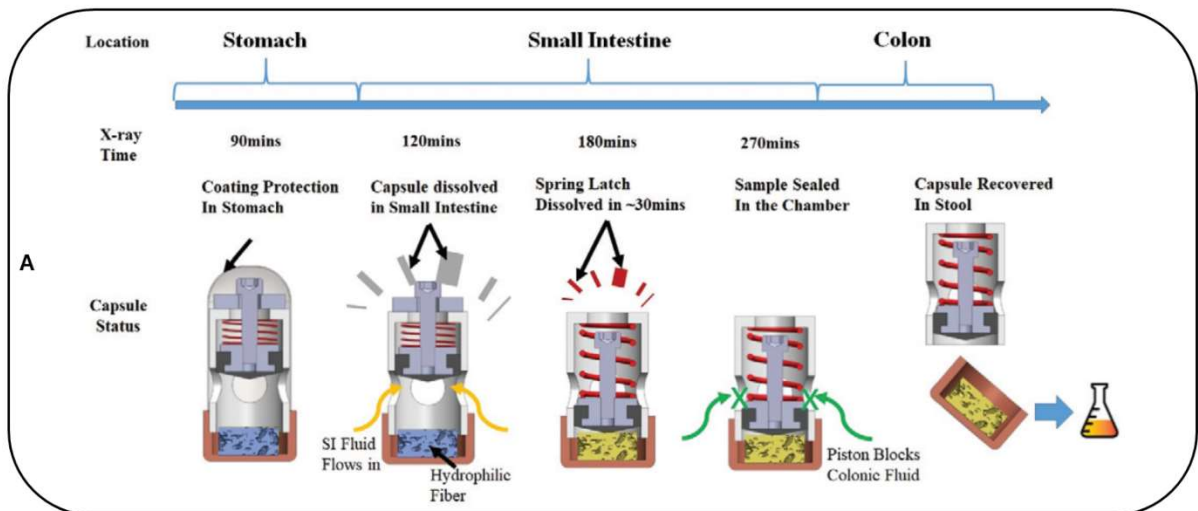
1 sensor was used to determine the pill's location along the GI tract, and the stepper motor was used to actuate a  
2 piston that pushed out the reservoir contents. [88], F) The 34 mm long and 11 mm diameter Enterion capsule  
3 contained a 1ml internal drug reservoir, as well as a separate reservoir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



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

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



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

1 prevent further fluid exchange. The hydrogel encapsulated sample can be retrieved due to the screw cap design  
2 [202], D) Osmotic microbiome sampling pill is primed by injecting water into the salt chamber and the helical  
3 channels. The capsule is enterically coated before ingestion to protect it from the stomach. The integrated magnets  
4 allow the capsule to be held in a specific part of the GI tract. Osmotic pressure induced flow occurs along the helical  
5 channels through the semipermeable membrane, drawing microbiota in. [201]