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Controlled colonic insufflation by a novel remotely-triggered capsule enables complete mucosal visualization (with video)

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Abstract:	Background and study aims: Capsule endoscopy is an attractive alternative to colorectal cancer screening by conventional colonoscopy, but is currently limited by compromised mucosal visibility, secondary to an unmet need of safe, controlled colonic insufflation. We have therefore developed a novel system of untethered, wireless controlled carbon dioxide (CO2) insufflation for use in colonic capsule endoscopy, which this study aims to assess in-vivo. Subjects and methods: This is an observational study of in-vivo non-survival Yorkshire-Landrace cross swine. After placement of a novel insufflation capsule in the porcine colon, we recorded volume of insufflation, time, force, visualization, and a pathologic assessment of the colon. Results: In-vivo trials demonstrated a mean diameter of insufflation of 32.1±3.9 mm. The volume of CO2 produced successfully allowed for complete endoscopic visualization of the mucosa and for safe proximal passage of the endoscope. Pathologic examination demonstrated no evidence of trauma secondary to the capsule. Conclusions: These results demonstrate the feasibility of a novel method of controlled colonic insufflation via an untethered capsule in-vivo. This

	technological innovation addresses a critical need in colon capsule endoscopy.
Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.	
Video 1.mov	

Introduction

Colorectal cancer (CRC) is the third most common cancer in both men and women and the second leading cause of cancer death in the United States [1]. CRC is also one of the most preventable as it has a well-defined pre-malignant phase that can be readily detected and removed using endoscopic techniques [2-5]. Colonoscopy remains the "gold standard" for CRC screening due to its safety and effectiveness. Yet its benefits have not been realized by a significant proportion of the population—in 2009 only a little over 60% had received appropriate screening, as compared with breast cancer (more than 70%) or cervical cancer (80% or more) [1]. Many factors may account for this including a disruptive and time consuming process (patients generally have to miss a day of work and must have a companion to assist with transportation back to their residence), the potential for pain, and the small risk of adverse events [6]. Thus there is a clear need for improved and more acceptable methods for CRC screening.

In this regard, capsule endoscopy is a very attractive alternative to colonoscopy, and is now an essential tool for evaluation of patients with suspected small-bowel disorders [7,8]. As technology around small-bowel wireless capsule endoscopy advances, a natural progression has been toward its adaptation for examination of the colon [9]. Unfortunately, in its current embodiment, the sensitivity and specificity for detection of colon lesions is disappointingly low (sensitivity=73%, specificity=89%) [10]. In conventional colonoscopy, visualization of the mucosa is improved by insufflation of the colon; with a positive correlation between luminal distention achieved by insufflation and polyp and adenoma detection rate [11]. One factor contributing to the suboptimal performance of colon capsule endoscopy is partial or incomplete visualization of the mucosa during the exam. Thus, there is a need for similarly safe, controlled, and reliable insufflation in colon capsule endoscopy.

Our team has been working on a highly innovative approach to address this critical technological gap. We have developed a novel device to achieve untethered controlled carbon dioxide (CO_2) insufflation suitable for capsule endoscopy of the colon: the CO_2mfort Cap. CO_2 has been advocated as a substitute to traditional room air due to its advantages of reduced post-procedure gas secondary to its rapid absorption, as well as improved patient comfort secondary to an overall decrease in intestinal distention [12,13]. Our seminal reports of this technology provided bench-top and *ex-vivo* demonstration of the ability of the CO_2mfort Cap to produce adequate CO_2 volumes for complete visualization of the colonic mucosa [14,15]. In this study, we examined the feasibility and safety of this device *in-vivo*.

Materials and methods

Description of CO_2mfort Cap

The CO_2mfort Cap is a novel two-compartment capsule containing reactants that when mixed, yield CO_2. The basic chemical reaction uses FDA-approved products [16] sodium bicarbonate ($NaHCO_3$) and citric acid ($C_6H_8O_7$) to produce sodium citrate ($Na_3C_6H_5O_7$), carbon dioxide (CO_2), and water (Fig. 1). Fabricated from a polypropylene-like material (Objet DurusWhite RGD430, Billerica, MA, USA), the CO_2mfort Cap is 12 mm in diameter and 32 mm in length, comparable in dimension to 11 mm x 31 mm Pillcam Colon (Given Imaging, Inc., Yoqneam, Israel). The CO_2mfort Cap has two separate compartments connected by two magnetic valves (Fig. 2). When activated, the citric acid solution in the upper compartment reacts with the sodium bicarbonate in the lower compartment, producing CO_2 that is released through the exhaust ports along the lower midline of the capsule. Remote triggering is achieved by means of a disc-shape NdFeB external permanent magnet (EPM) (Sintered NdFeB magnets, B&W Technology and Trade GmbH, Jena, Germany) with a diameter of 50 mm, thickness of 20 mm, and a N52 axial

magnetization.

Bench-top trials to assess reaction kinetics
Previous experiments of the chemical reaction were performed at room temperature [18]. To determine the performance at standard body temperature, we conducted ten bench-top trials at 37°C**.** For each trial, a total of 0.82 grams $NaHCO_3$ and 0.63 grams $C_6H_8O_7$ were utilized in 0.75 ml water. Measured parameters included: volume of CO_2 produced via the water displacement technique, time to reach 50% of the CO_2 plateau (t_{50}), and time to reach the CO_2 plateau ($t_{plateau}$).

Bench-top trials to assess force generation and safety
To determine the maximum force that may be exerted on the colon mucosa by the capsule secondary to the magnetic couple between the internal and external magnets, we conducted a simple experiment. A CO_2mfort Cap was attached to a load cell (Nano 17, ATI Industrial Automation, Apex, NC, USA) and an N52 EPM measuring 50 mm by 20 mm was placed 200 mm above the center of the capsule. As the EPM was moved toward the CO_2mfort Cap, the force generated by magnetic coupling and the distance between the CO_2mfort Cap and EPM were recorded.

In-vivo porcine trials
Based on our prior *ex-vivo* data, we tested the ability of multiple CO_2mfort Caps to work in synergy in order to optimize luminal visibility *in-vivo*. Five separate swine each underwent per-rectum placement of three CO_2mfort Caps. Experiments were performed in five female Yorkshire-Landrace cross swine weighing 30-35 kg. General anesthesia was induced with Telazol (4.4 mg/kg IV, Fort Dodge, Ames, Iowa), xylazine (2.2 mg/kg IV), and ketamine (2.2 mg/kg IV). Following endotracheal intubation and throughout the procedure, the animals were maintained on a semi-closed circuit inhalation of 1% to 3% isoflurane and ventilated.

The three capsules were placed in close enough proximity to allow for simultaneous activation of the reaction by the EPM. All reactions were observed under direct endoscopic visualization (the endoscope was disconnected from air insufflation and suction) and by fluoroscopy for a period of 12 minutes. Fluoroscopic images were acquired to estimate the diameter of the gas column generated (cm) and sustained. These measurements were analyzed by ImageJ software (National Institute of Health, Bethesda, MD, USA). Using the known diameter of the endoscope (GIF 160; Olympus, Tokyo, Japan) of 12.9 mm, the scale was set at 4.496 pixels/mm. The column of CO_2 was modeled as a cylinder, divided into a series of sections at equal intervals, and the diameters were recorded. These were then averaged to estimate the diameter of the gas column generated per trial.

The animal was sacrificed upon procedural completion. The colon was then explanted and examined by an expert gastrointestinal pathologist. The study was approved by the local Institutional Animal Care and Use Committee.

Statistical Analysis
All continuous data are reported as mean±standard deviation (SD). Normally distributed continuous variables were analyzed using a *t*-test. ANOVA was utilized to compare bench-top reaction kinetics to *in-vivo* reaction kinetics using Prism6 (GraphPad Software Inc., La Jolla, CA, USA). Statistical significance was set at $p<0.05$.

Results

CO_2 production reaction is rapid and robust

We first tested the reaction kinetics and performance characteristics *in vitro*. Bench-top reaction testing at 37°C yielded a mean CO_2 volume of 286.64±11.80 ml at t_{50}=1 minute and 509.01±9.35 ml at $t_{plateau}$=12 minutes

External permanent magnet produces a modest but measurable force on the capsule
When the distance between the capsule and EPM is 78.7±6.0 mm, the force generated by magnetic coupling is sufficient to overcome the weight of gravity on the capsule. When the distance between the capsule and EPM is reduced to 52.5±2.5 mm, the force generated by the magnet is sufficient to activate the valves. As the distance between the capsule and EPM approaches zero, the force generated by the magnet couple approaches 1.025 N. If this force is distributed across the upper surface of the capsule, as defined by 1/3 of the total surface area, the maximum pressure placed on the colon is 2458.91 pascals (0.025 bar).

CO_2 production in vivo occurs in a controlled and effective manner
In all five *in-vivo* porcine trials, the CO_2mfort Caps were successfully triggered and insufflated the porcine colon without evidence of perforation or free air as demonstrated by fluoroscopy**.** Fluoroscopic image analysis demonstrated experimental reaction kinetics that were similar to bench-top trials (p=0.28). The maximum insufflation diameter achieved was 32.1±3.9 mm by 540±53.7 seconds (Fig. 3).

Complete visualization of the colon is safely enabled by the CO_2mfort Cap
The lumen distention achieved was sufficient for complete endoscopic visualization of the mucosa and safe proximal passage of the endoscope under direct visualization (Video 1). All swine survived and there were no intra-operative or immediate post-operative adverse events. On gross pathology examination, there was no evidence of perforation and there was no evidence of microscopic trauma in three of five specimens (Table 1). Specimens 2 and 3 each demonstrated a linear red streak that corresponded to mild microscopic sub-mucosal edema and a patchy area of hemorrhage into the lamina propria and submucosa.

Discussion

This study has several important results with both technical and clinical implications. We chose to test three CO_2mfort Caps simultaneously in our *in-vivo* trials as our bench-top data indicated that a single CO_2mfort Cap produces roughly half a liter of insufflation. We attribute the comparable estimated volume produced by three capsules in-vivo to loss of CO_2 via the rectum and absorption by the colon mucosa. Nevertheless, in this manner, we were able to demonstrate that when multiple capsules are used in conjunction, they do not stick together and do not self-activate (as the force between the magnetic sphere and metallic ring is stronger than the force between any adjacent magnet from other nearby capsules). Thus, if further insufflation is needed during endoscopy, our approach provides the possibility of introducing additional capsules per rectum to achieve the desired result.

We have designed the CO_2mfort Cap flow gate with the capacity to trigger the reaction in aliquots. In order to trigger the reaction, the maximum allowable distance between the EPM and CO_2mfort Cap internal magnets was 52.5±2.5 mm. Bringing the EPM within this distance from the capsule triggers the reaction by opening the flow gate. When the external magnet is taken away from the capsule, the flow gate closes and the reaction stops. This distance can be easily varied depending on the size and strength of the external magnet utilized. For different patient populations, including obesity, larger external magnets can create a stronger magnetic field to allow for control of the release-trigger. Such a design can assist the physician to optimally control insufflation on an as-needed basis.

Although 2-dimensional measurement approximations from the fluoroscopic images do not allow for an accurate estimate of volume produced per capsule *in vivo*, we were able to demonstrate that the reaction kinetics based on diameter are similar to bench-top trials for volume. Assuming the *in-vivo* yield was nonetheless lower than bench-top trials, the CO_2mfort Cap was interestingly capable of allowing full mucosal visualization for the duration of the procedure with relatively little CO_2.

Our system currently has the capacity to exert a maximum pressure of 0.025 bar against the colonic mucosa. Pressure up to 3 bar result in no mucosal damage to the colon [17]. In this study, the colons of two of the five swine demonstrated submucosal edema and a patchy area of hemorrhage into the lamina propria and submucosa (Table 1). The diameters of the linear marks are congruous to the diameter of the endoscope and are most consistent with trauma secondary to the endoscope coming in contact with the colon and not due to the CO_2mfort Cap or the reaction itself. These findings can also be seen in colonoscopy and are generally not considered clinically significant.

The CO_2mfort Cap is designed such that as long as the compartments remain tightly sealed, the shelf-life is theoretically determined by the manufacturer's recommended care of the reactants. Sigma recommends re-testing sodium bicarbonate (Sigma S5761) every 3 years while citric acid (Sigma C2404) requires no re-testing. Inadvertent or premature exposure to a strong magnetic field has the potential to open the flow gate, allowing reactants to mix. Precautions against this must be taken and are in development (e.g., a shielded container can be used to store the capsules). Other limitations of our study include the use of an *in vivo* non-survival porcine model and a small experimental sample size. This design was chosen due to the nature of the study aims: *in-vivo* feasibility and safety evaluation. We note that just as in conventional colonoscopy, thorough bowel prep is needed to ensure efficacy of capsule endoscopy utilizing the CO_2mfort Cap. Finally, while our prototype was manufactured from a polypropylene-like material due to ease of availability, the capsule can be readily fabricated out of a biocompatible material such as polyether ether ketone (PEEK).

The CO_2mfort Cap also has the exciting potential to address another critical need in colon capsule endoscopy—the ability to be actively propelled along the colon rather than move passively, as colonic transit time in healthy people can be 20-56 hours [18]. A future direction for our team is to achieve both insufflation and controllable motion at the same time, as can be obtained with variations in the design of the magnetically controlled valves.

In conclusion, this is the first *in-vivo* demonstration in the literature of a technique that adds an exciting dimension to colon capsule endoscopy; namely, the ability to distend and visualize the colon on demand with an untethered approach. Using a highly innovative design, we safely and reliably remotely triggered a chemical reaction within the CO_2mfort Cap. This released CO_2 in a controlled fashion and allowed for clear mucosal visibility with a colonoscope. We envision that such insufflation may allow for better visualization of colonic lesions and increase the diagnostic yield of colon capsule endoscopy. These results have important implications for the future of capsule endoscopy and could potentially be transformative for how we screen patients for CRC.

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vivo experiment.

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Figure and Video Legends:

Figure 1. Chemical reaction utilized by the CO_2mfort Cap to form carbon dioxide from sodium bicarbonate, citric acid, and water.

Figure 2. In the CO_2mfort Caps closed configuration, the magnetic valves form a tight barrier between its two compartments. When triggered by an external permanent magnet, the valves open to allow for mixture of the two reactants, producing CO_2 released through exhaust ports along the lining of the lower compartment.

Figure 3, Endoscopic view and corresponding fluoroscopic images over the course of *in-vivo* trial 3. Fluoroscopic images were acquired and transmitted in real-time to a monitor while endoscopic visualization of the distal colon lumen was performed to confirm mucosal visibility.

Video 1, Demonstration of in-vivo capsule insufflation.

Table 1, Pathology results of *in-vivo* porcine trials.

Trial	Gross	Microscopic
1	Focal surface erosion	Patchy accumulation of neutrophils in lamina propria with a few crypt abscesses.
2	Linear red streak	Patchy area of hemorrhage into lamina propria and submucosa, with neutrophils and loss of mucin. Submucosal edema.
3	Linear red streak	Patchy area of hemorrhage into lamina propria and submucosa, with neutrophils and loss of mucin. Submucosal edema.
4	Normal	Small patch of neutrophils in superficial lamina propria (mild)
5	Normal	Normal

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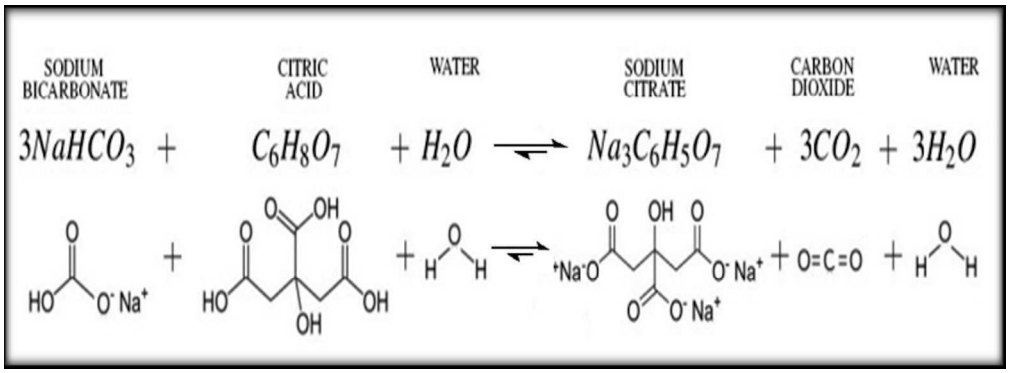

Figure 1. Chemical reaction utilized by the CO2mfort Cap to form carbon dioxide from sodium bicarbonate, citric acid, and water.
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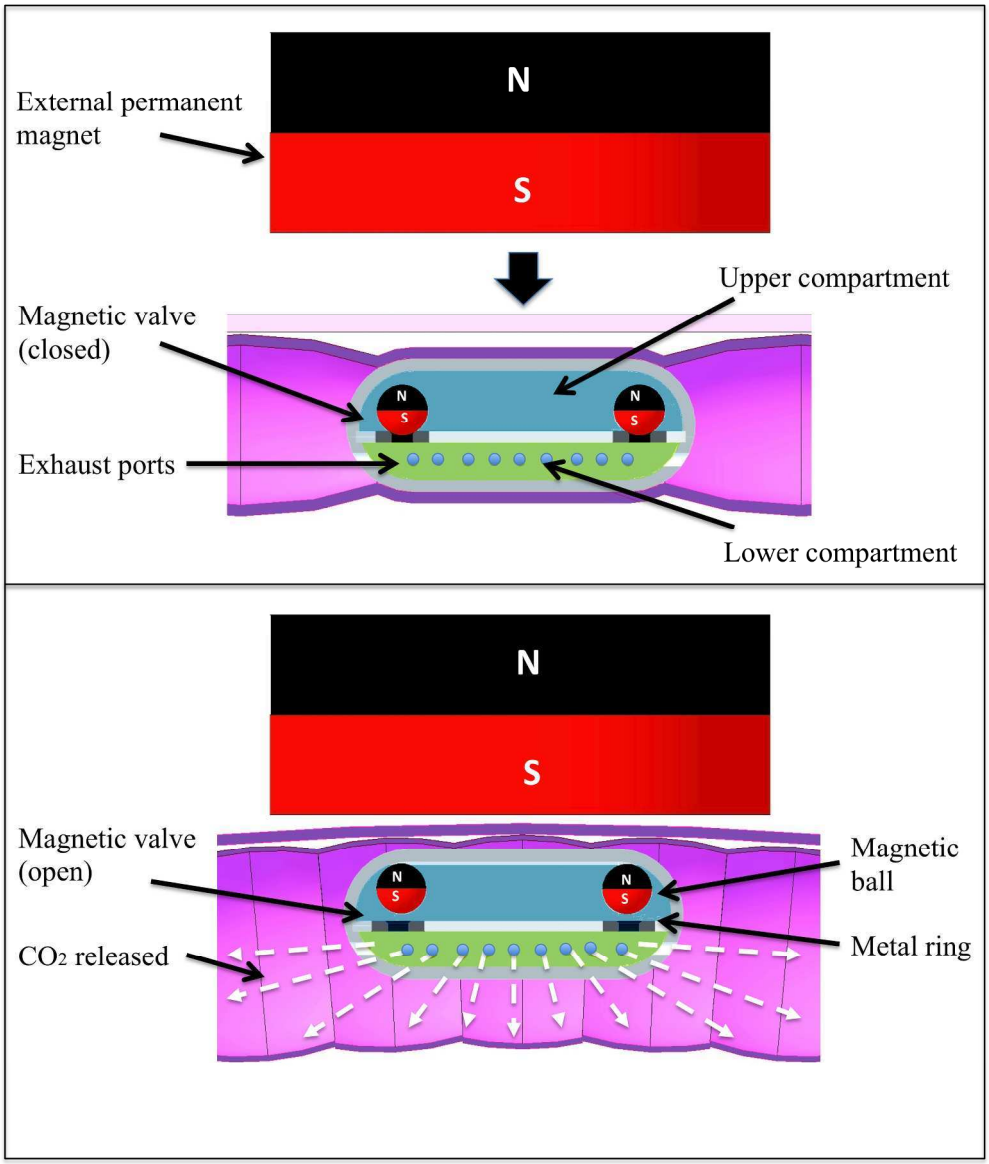

Figure 2. In the CO2mfort Cap's closed configuration, the magnetic valves form a tight barrier between its two compartments. When triggered by an external permanent magnet, the valves open to allow for mixture of the two reactants, producing CO2 released through exhaust ports along the lining of the lower compartment.
221x259mm (300 x 300 DPI)

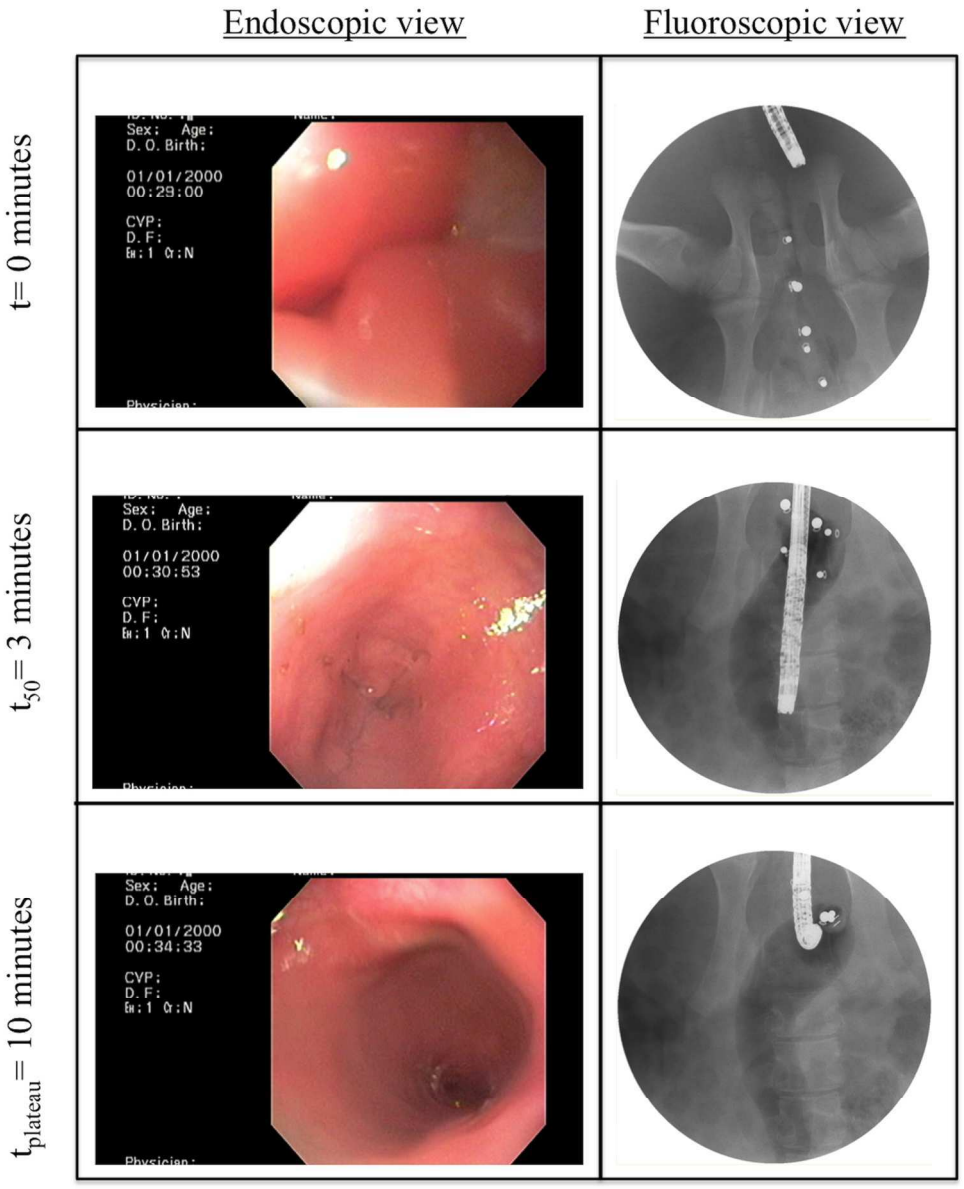

Figure 3. Endoscopic view and corresponding fluoroscopic images over the course of in-vivo trial 3. Fluoroscopic images were acquired and transmitted in real-time to a monitor while endoscopic visualization of the distal colon lumen was performed to confirm mucosal visibility.
152x182mm (300 x 300 DPI)