# Intra-luminal focused ultrasound for augmentation of gastrointestinal drug delivery

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The recent article by Schoellhammer *et al.*, "Ultrasound-mediated gastrointestinal drug delivery" primarily addresses practical limitations in drug delivery for medical management of inflammatory bowel disease (IBD), and presents pre-clinical data demonstrating that intra-luminal, sub-ablative focused ultrasound (FUS), delivered via a trans-rectal transducer, can overcome some of these limitations (1). The clinical application and benefit of such a device is clear. Currently, outpatient treatment of proctitis/proctosigmoiditis can involve patient self-administration of an anti-inflammatory drug enema (e.g., mesalamine, hydrocortisone) that is ideally retained overnight to maximize medication absorption (2,3). Compliance with this regimen can be highly challenging for patients with active colitis as symptoms include urgency and frequent bowel movements. Methods to improve the efficiency of drug transit/tissue penetration and thus decrease both the frequency of enema administration as well the required mucosal exposure time to the enema would likely be welcomed by patients. Improved compliance on this more rapid regimen could theoretically help to mitigate the long-term sequelae of under-treated disease. An important question raised and discussed in this article is how to expand upon this particularly well-suited clinical application to improve targeted drug delivery (TDD) to other areas of the gastrointestinal (GI) tract.

*Ex vivo* experiments were performed on samples of tissue taken from throughout the porcine GI tract. These were mounted and exposed to variable, relatively low intensity ultrasound frequencies followed by quantification of delivery of permeants (e.g., glucose, dextran, insulin). Treated tissues showed enhanced transport. Similar findings were demonstrated in small and large bowel tissue for radiolabeled mesalamine and hydrocortisone. With 1 minute of ultrasound treatment time, 3–5-fold improved drug delivery was observed versus control. Additional *ex vivo* experiments utilizing variable FUS protocols to alter the thermal, radiative force, and cavitation effects of FUS therapy demonstrated drug delivery to be enhanced primarily through transient cavitation effects.

*In vivo*, both pigs and mice were used to assess the safety and efficacy of treatment with trans-rectal FUS transducer models. These studies revealed no evidence of ultrasound-induced injury, a ~22-fold increase in mesalamine uptake in treated tissue with concurrent mesalamine enema, and effective ultrasound-driven absorption and systemic response to concurrent insulin enema. A mouse model of dextran sodium sulfate induced colitis showed significantly faster recovery (assessed by total fecal score and histologic response) in mice treated with either daily or every-other-day FUS and mesalamine enema versus daily enema alone. These results support the idea that clinical application of FUS-augmented mesalamine enema in IBD can improve both drug transit/tissue penetration, as well as clinical outcomes for patients with poor tolerance of daily enemas during active disease flares. Further large animal studies, as the authors suggest, will facilitate safe and effective transition of this technology to clinical treatment of IBD.

Application of FUS directly to the GI mucosa has new and exciting implications for TDD. Research regarding FUS-mediated TDD has surged in recent years, with notable examples including transient blood-brain-barrier disruption to enable brain parenchymal or tumor delivery of drugs (4), as well as bodily-tumor targeted FUS to augment local small molecule delivery (e.g., chemotherapy agents) (5). Drug penetration and absorption through the GI mucosa, however, has received little attention prior to the study in question. Importantly, beyond the rectal application most thoroughly explored in this article, enhanced drug delivery was demonstrated with FUS therapy throughout the GI tract *in vitro*, opening the door for additional studies exploring methods to effectively deliver FUS therapy *in vivo* to these other locations.

FUS-enabled endoscopic devices have been developed and employed to target both the GI mucosa and the hepato-bilio-pancreatic systems through the wall of the intestinal lumen, typically for ablation of malignant/pre-malignant lesions, but also to enhance TDD to tumors (6,7). Endoscopic FUS, however, is impractical to enhance delivery of most orally-ingested medications, which require repeated dosing. The development of a non-invasive, convenient and cost-effective means of FUS delivery to the entirety of the GI mucosa for enhanced drug delivery would revolutionize modern medical treatment—allowing effective systemic delivery of multiple compounds that have minimal mucosal penetrance under normal physiologic parameters, or in pathologic malabsorptive conditions. The authors raise the interesting possibility of developing ingestible, ultrasound-emitting tablets that could augment therapeutic drug delivery throughout the GI tract. Development of such a device would present unique challenges, as its efficacy in successfully and safely generating cavitation would be highly variable during transit, and likely extremely limited in areas where there was a significant amount of intraluminal bowel gas. This latter limitation was effectively mitigated in the current study by delivery of a liquid enema to the rectal lumen, minimizing air foci between the trans-rectal FUS transducer and the GI mucosa. That said, with appropriate dietary restrictions, therapeutic benefit could be achieved with such a device, and we look forward to reading about future developments toward this end.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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