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Capsule-based Ultrasound-mediated Targeted Gastrointestinal Drug Delivery

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***Abstract*—Diseases which are prevalent in the gastrointestinal (GI) tract, such as Crohn's disease, are a topic of increasing concern because diagnosis and specific treatment are difficult and may be ineffective. New techniques are therefore sought after and this paper describes a proof-of-concept tethered capsule for targeted drug delivery (TDD) in the GI tract. The capsule consists of a camera, illumination, a drug delivery channel and an ultrasound (US) transducer. The transducer is described in detail, including a comparison of different piezoceramic materials that has been carried out. It was found that PZ54 (Ferroperm Piezoceramics, Kvistgaard, Denmark) was the most suitable material for our application. When driven at 4 V_{pp}, the outer diameter 5 mm PZ54 transducer operates at a frequency f = 4.05 MHz providing an acoustic pressure, P_{ac} = 125 kPa, with a beam diameter, BD = 0.75 mm at the focus. Pressures in the range 50 – 300 kPa have been previously reported as suitable for sonoporation, a process vital in many TDD applications, so this is a promising result. Basic functional testing of the capsule was performed by supplying glass microbubbles (MBs) through the drug delivery channel into the US focus, monitored via the on-board camera. It was found that the acoustic radiation forces have a clear influence on the MBs, significantly changing their direction at the US focus. This suggests that drugs may be targeted to specific tissue in the GI tract by the new capsule. The results translate into a capsule configuration with the potential to be clinically and biologically useful.**

Keywords—Therapeutic Capsule; Targeted Drug Delivery; Ultrasound Capsule; Capsule Endoscopy; UmTDD; GI Drug Delivery

I. INTRODUCTION

Capsule endoscopy (CE) for diagnosis in the gastrointestinal (GI) tract has emerged over the last fifteen years. Now established in commercial products from companies such as Olympus (Olympus Corporation, Tokyo, Japan) and Covidien (Covidien Ltd., Dublin, Republic of Ireland) and documented as having benefitted more than one million patients, it is a clear candidate for further innovation for both diagnosis and therapy.

Ultrasound (US) is used extensively in medicine as a minimally-invasive and low-cost diagnostic imaging tool. Over the last few decades, there has been a growing research interest in the use of US in therapeutic applications, such as focused ultrasound (FUS) surgery and ultrasound-mediated targeted drug delivery (UmTDD) [1 - 2]. An additional beneficial factor in drug delivery (DD) applications is the inclusion of gas-filled microbubbles. These microbubbles, whose initial application was as an agent for imaging contrast enhancement, become active when sonicated, inducing US cavitation. This has the potential to cause clinically useful biological effects such as shock waves and sonoporation, which can, in turn, increase cell membrane permeability to bioactive materials [3 - 4].

In UmTDD, microbubbles loaded with drugs or nanoparticles and used in combination with US have been shown to facilitate cellular delivery and uptake [3, 5 - 7]. Moreover, applying US in the presence of microbubbles has been shown to simultaneously increase cell membrane permeability, i.e. Sonoporation, and release or trigger therapeutic drugs at the target site. This has potential for minimally-invasive and localised therapy greatly increasing the efficacy of the drug or agent at the target site while simultaneously reducing unwanted systemic effects such as toxicity to healthy tissue [6, 8 - 10].

Taking this into consideration, the aim of the work described here was to design, construct and test a proof-of-concept capsule for the therapy of GI conditions such as Crohn's disease. In this capsule, the applied US would have three functions: to direct drugs and their packaging to the target, to release the drugs from the packaging, and to increase uptake through sonoporation. Here, the components in the capsule will be discussed in turn, with a detailed focus on the transducer, comparing different piezoceramic materials considered for inclusion in the capsule.

II. Materials and Methods

This section describes the comparison between the piezoceramics considered for the transducer and outlines the transducer fabrication process. The design of the capsule and a discussion of the remaining components are provided. This section is concluded by discussing the functional testing carried out with the capsule.

A. Transducer Fabrication

Different piezoceramic materials were identified as candidates for the transducer to be embedded in the capsule. The two materials chosen for further study were PZ54 and PZ26 (Ferroperm Piezoceramics, Kvistgaard, Denmark). PZ54 is a piezoceramic specifically designed for FUS applications and PZ26 represents the piezoceramic material most commonly used in FUS applications. To better determine which material would be most suitable for capsule inclusion transducers were fabricated and characterised with both of them.

The specific piezoceramic geometry studied is a self-focusing bowl with an outer diameter, OD = 5 mm, and radius of curvature, R_c = 15 mm. The backing layer used for the transducer is a composite of microbubbles (K1 Glass Bubbles, 3M) and epoxy (Epofix, Struers A/S, Denmark) mixed at a ratio 3:1 by weight, formed into the desired shape by using a PTFE mould. The backing layer is formed so that the outer shell of the transducer has OD = 6 mm and length = 4 mm. The coaxial cable used to attach the transducer to the signal generator has diameter 300 µm, connected to the transducer with Ag-loaded epoxy and to the driving signal generator with a BNC connector. A fabricated transducer can be seen in Fig. 1 with backing layer and cable.

B. Capsule Design and Components

The capsule has four main features: FUS transducer, CMOS imaging camera and illumination, drug delivery channel and a tether for control. The design of the capsule is such that the transducer, camera and drug delivery channel are confocal at approximately 4 mm from the capsule perimeter. The reason the components are confocal at 4 mm is that this is the assumed location of the bowel wall. If the distance was any greater, the transducer might focus beyond the bowel wall, which could result in too low an intensity of US. Of course, this fixed focus may also cause problems if the bowel wall is irregular.

The capsule was designed using SolidWorks (Dassault Systemes SolidWorks Corp., Velizy-Villacoublay, France) and

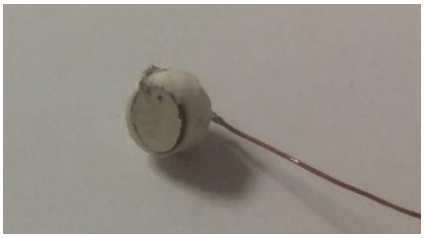

Fig. 1: Fabricated PZ54 transducer with OD = 6 mm and length = 4 mm. 0.3 mm coaxial cable attached.

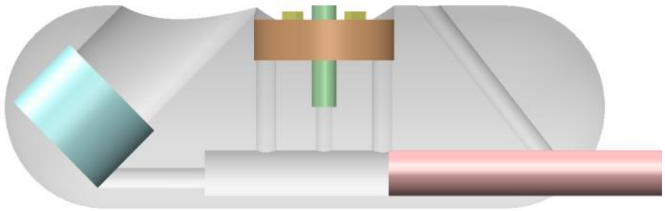

Fig. 2: Rendered CAD drawing of capsule. Components (from left-to-right) are: Transducer, Illumination, camera and tether with drug delivery channel.

3D printed using an Objet Connex 500 (Stratasys Ltd., Minnesota). The capsule is 10 mm in diameter and 30 mm in length, this size chosen so that the capsule is comparable in size with capsules used for video endoscopy and other purposes. The design of the capsule is shown in Fig. 2.

The camera chosen for capsule inclusion is the Medigus Micro ScoutCAM 1.2 (micro ScoutCam™, Medigus Ltd., Israel) which has OD = 1.2 mm and length = 5 mm. The camera cable has a diameter of 0.8 mm. A dedicated digital signal processor controls the camera. The illumination consists of a printed circuit board (PCB) with four white light emitting diodes (LEDs) controlled by a direct current (DC) power supply. The PCB has OD = 7 mm and thickness = 2.2 mm, with a hole diameter = 1.4 mm in the centre for the camera to pass through. The drug delivery channel is a fine-bore polythene tubing with OD = 0.96 mm and is controlled by a syringe pump external to the capsule. These components can all be seen in Fig. 3.

C. Functional Testing

To assess the capsule's functionality in UmTDD applications, tests were performed using the capsule set up as described above.

In order to align the camera, air filled glass MBs were passed through the drug delivery channel and into the camera's field of view. The camera was then adjusted until the microbubbles were central in the field of view.

The main functionality test carried out was to pass MBs through the drug delivery channel and into the US focus, while their behaviour was observed with the camera. The MBs were used to simulate drug-filled MBs which are commonly used in UmTDD applications. If the US can move around MBs then this is an early indication of its potential to target the MBs at a specific position on the surface of the tissue and to externalise their contents.

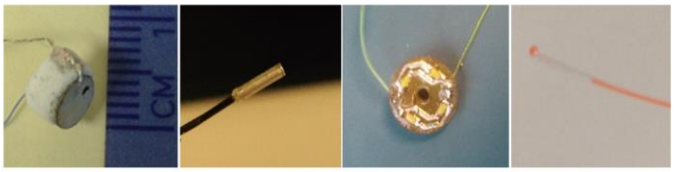

Fig. 3: Capsule components (from left-to-right) are: US transducer, Medigus Micro ScoutCam camera, illumination and drug delivery channel with red dye for visibility.

III. RESULTS

A. Characterisation Results and Transducer Comparison

Characterisation of the PZ54 and PZ26 transducers is an important step because it allows further differentiation between the two transducers to determine the best candidate for inclusion in the capsule.

The first step in the characterisation process is impedance spectroscopy, to identify the optimum frequency for driving the transducer, called the central driving frequency (CDF). The impedance was measured after each fabrication step using a 4395A Impedance Analyser (Agilent Technology / Keysight, Santa Clara, CA, USA). It was found that the CDF of the PZ54 transducer was 4.05 MHz, close to the figure stated by the manufacturer. The impedance magnitude of the fully fabricated transducer was found to be suitably close to the 50 Ω impedance of the wire so electrical impedance matching was not required.

The next step in the characterisation process is US field mapping. This was carried out using a calibrated needle hydrophone (Precision Acoustics, Dorchester, UK) scanned in the US field in an acoustic scanning tank (Precision Acoustics, Dorchester, England). These measurements allowed the acoustic pressure from and beam diameter of the transducers to be determined. Both transducers were driven at their CDF with V = 4 V_{pp} from a signal generator with a 50 Ω output. The pressure mapping of the PZ54 transducer is shown in Fig. 4, indicating P_{ac} = 125 kPa and focal beam diameter, BD = 0.75 mm. In comparison, the PZ26 transducer provided P_{ac} = 157 kPa BD = 1.35 mm.

At this stage, enough data was available for a useful comparison of the transducers. Literature states that pressures in the range 50 - 300 kPa are suitable for reversible sonoporation in the GI tract [11]. Both the PZ26 and PZ54 transducers can provide pressures in this range. The PZ54 transducer was therefore selected as its smaller BD would allow a smaller area to be sonicated. Also PZ54 is more suitable for FUS purposes because it has a higher permittivity than PZ26, making it better for electrical impedance matching.

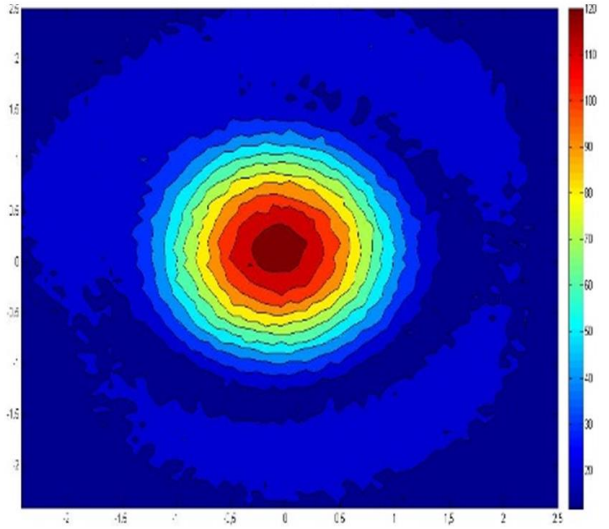

Fig. 4: US pressure mapping which shows the PZ54 outputs and acoustic pressure, P_{ac} = 125 kPa, with focal beam diameter, BD = 0.75 mm.

Fig. 5: (Purple arrows in each case represents direction of travel of MBs) Left: MBs approaching US focus. Middle: MBs reaching the US focus, beginning to change direction. Right: MBs completely changing direction due to acoustic radiation forces.

Further characterisation of the PZ54 transducer was then carried out with the next step using a thermal camera to measure the temperature rise of the transducer and cable during operation. The thermal camera was focused on the face of the transducer and the cable in turn; it was found that there was no significant temperature rise at the transducer face or along the cable.

The final characterisation procedure was acoustic power measurement. This was carried out using a radiation force balance (Precision Acoustics, Dorchester, UK) awith the PZ54 transducer driven at different input voltages. It was found that at driving the transducer at V = 4 V_{pp}, acoustic power = 20.45 mW is produced which increases linearly up to P = 85 mW at V = 10 V_{pp}.

B. Experimental Results

It was also considered useful to carry out functional testing to show the influence of the acoustic radiation force from the PZ54 transducer on a stream of MBs from the drug delivery channel. The capsule was set up with the PZ54 transducer along with camera, illumination and DD channel. MBs were used as before, with an average diameter of 65 µm, delivered using a syringe pump (BRAUN perfusor FM Pump IV Infusion syringe pump B, Braun Medical Ltd., Sheffield, UK). The US transducer driven at 7 V_{pp} at CDF = 4.05 MHz and the corresponding results are shown in Fig. 5. Fig. 5 (left) shows the MBs approaching the US focus and Fig. 5 (right) shows the MBs after they have changed direction due to the acoustic radiation force. These results are promising as they highlight the influence of the US on the MBs. This shows early indication that this capsule configuration could be suitable for clinical procedures involving drug-loaded microbubbles being trapped against the bowel wall, releasing their contents into sonoporated cells due to the US force.

IV. Conclusion

This paper has discussed a proof-of-concept tethered capsule for therapy in the GI tract. The capsule has a diameter OD = 10 mm and length = 30 mm, making it comparable in size with commercial capsules for video endoscopy. The capsule includes a camera with illumination, drug delivery channel and US transducer in a shell made with 3D printing.

Different transducers materials, PZ54 and PZ26, have been considered for capsule inclusion. Both transducers were characterised, beginning with electrical impedance measurements. From the impedance measurements it was found that both transducers have a CDF close to that stated by the manufacturer and it was found that no electrical impedance matching was required. US field mapping was then carried out and it was found that, when driving the transducer at 4 V_{pp}, the PZ54 transducer has an acoustic pressure, P_{ac} = 125 kPa and focal BD = 0.75 mm while the PZ26 transducer has P_{ac} = 157 kPa and focal BD = 1.35 mm. The pressure outputs are in the 50 kPa - 300 kPa range suitable for Sonoporation in the GI tract [11], a process which plays a key role in many UmTDD procedures.

At this stage the PZ54 transducer was chosen for capsule inclusion, mainly because of its narrower BD resulting in a smaller area of sonication but also since PZ54 has a higher permittivity than PZ26 making it better for FUS. Further characterisation of the PZ54 transducer was then carried out. Thermal testing showed that the transducer and cable do not heat up significantly at 4 V_{pp}. Acoustic power measurements were also carried out and at 4 V_{pp} an output acoustic power = 20.45 mW was recorded.

Once characterisation of the transducer was complete, the capsule was assembled for functional testing. The most important test involved glass MBs flowing through the drug delivery channel into the US focus, with their behaviour monitored using the camera. It was found that the PZ54 transducer the behaviour of the MBs using the camera. It was found that the PZ54 transducer had the ability to alter the direction of travel of the MBs, promising results for drug delivery applications.

The two main results; the acoustic pressure being suitable for sonoporation in the GI tract and the transducer able to affect the MB egress suggests that a capsule configured as we have has potential in biomedical and drug delivery applications.

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