

A smarter SMA technology for the realization of drug delivering endoscopic capsule

Shagufta Murad, Javaria Murad, Hammad Khan

Khan Research Laboratories, Islamabad, Pakistan, Queen Elizabeth Hospital, Australia and University of South Australia

ABSTRACT

Traditional endoscopic and colonoscopic techniques are unable to access the small intestine for the delivery of biomarker probes and/or drugs. This is limiting the ability of medical researchers and practitioners to adequately explore the functional characteristics of the gastrointestinal tract (GIT), as well as the changes in the functional characteristics due to disease. This in turn is obstructing research for the development of newer biomarker probes and drugs for diagnosis and treatment of many conditions related to GIT. The advances in wireless capsule endoscopy have enabled

medical researchers to view the inside of the GIT. However, these devices are not capable of delivering biomarker probes and drugs to affected areas of the gastrointestinal tract. The prototype drug delivery mechanism presented in this paper is aimed at delivering a suitable technology for adoption in an endoscopic capsule for the administration of biomarker probes and/or drugs to targeted areas in the GIT. The design proposed in this paper is based on thermally actuated shape memory alloys. (Rawal Med J 2013;38:66-74).

Keywords: Endoscopic capsule; drug delivery; gastrointestinal tract; shape memory alloy.

INTRODUCTION

Historically the initial stages of endoscopic procedures took place in the early 1900s where the process consisted of the use of inflexible materials. But it was not until 1957 when fibre optic endoscopes were used.¹ Although a large degree of flexibility is achieved with the use of fibre optic scopes, it is still difficult to access distal parts of the small intestine via conventional endoscopic and colonoscopic techniques.² This is because the standard length of an endoscope is less than two metres³ whereas the GIT is approximately nine metres long. Although conventional endoscopy is a major approach to diagnose gastrointestinal disease, it has a complication rate of 0.432%, 0.228% and 2.016% for upper diagnostic gastrointestinal endoscopy, diagnostic colonoscopy and therapeutic colonoscopy, respectively.⁴ In 85% of endoscopic procedures there is the need to sedate the patient, which may result in complications.⁴ Even though endoscopy/colonoscopy is a vital tool for colorectal cancer diagnosis, 42.7% of patients aged 50 or more in the United States don't undergo any screening for fear of pain, sedation, embarrassment, and time involved in the tests.⁵

To overcome the above limitations some recent technologies, such as invendoscope SC40,⁶ double balloon endoscopy and wireless capsule endoscopy have been introduced. Due to smaller size and reduced complexity associated with wireless capsule endoscopy, numerous researchers have developed their own variations of wireless capsule endoscopes. For example, Given Imaging Ltd developed PillCam, Olympus Corp pioneered EndoCapsule and Intelligent Microsystem Centre introduced MiRO.⁷ However, none of these technologies address the unmet need for a device to deliver diagnostic biomarker probes or drugs directly to affected areas of the small intestine.

The small intestine, which is approximately six metres long, and is generally regarded by gastroenterologists as a black box particularly with respect to functional characteristics.⁸ This relative inaccessibility of the small intestine makes it difficult for medical practitioners to administer diagnostic drugs/biomarker probes⁹ directly to the affected area to determine the functional characteristics of the gut for diagnosis and treatment of a wide range of conditions. These include coeliac disease, small intestinal damage due to non-

steroidal anti-inflammatory drugs (NSAIDs), inflammatory bowel disease (IBD), irritable bowel syndrome (IBS) and chemotherapy-induced mucositis. Despite the recent advances in imaging technologies [9] to view the GIT, there is no device available yet for delivery of biomarker probes directly to areas in the GIT in a minimally invasive manner. There is a clear need for a low cost, disposable, minimally invasive endofunctional capsule that will enable medical researchers and eventually medical practitioners to administer diagnostic biomarkers to specific areas of the small intestine. Such a capsule will include (1) a biomarker delivery device, and (2) a tracking mechanism to track the location of the device in real time as it travels down the GIT.

A prototype solid-state micro machined drug delivery device was considered unsuitable due to the small volume it could support and also the complex manufacturing process involved.¹⁰ More recently, shape memory alloys (SMA) are finding increasing use as actuators in medical, safety, military and robotics applications.¹¹ Shape memory effect is the property which causes a material to remember its geometry at a specific temperature. It reverts back to its original shape when a characteristic stimulus is applied. Shape memory effect was first observed in Gold-Cadmium sample in 1932.¹² Then in 1962, William J. Buchler observed the same effect in Nickel-Titanium alloy (Nitinol).¹² It was observed that the shape memory effect in Nickel-Titanium alloy was due to a phase change between two states. The phase change between two solid states involves rearrangement of atoms within the crystal lattice. The low temperature phase is known as "martensite" and the high temperature phase is known as "austenite", with martensite having a highly twinned crystalline structure and austenite having a body centered cubic structure.¹²

The conventional shape memory alloys such as "Nitinol" are paramagnetic and the "martensite" change is caused by changing stress or temperature or both. In 1996 Robert O Handley and Ullakko observed a strain of 0.2% in NiMnGa when a magnetic field was applied.¹³ This led to a new generation of shape memory alloys called Ferromagnetic Shape Memory Alloys (FSMA),

which combined ferromagnetic properties along with shape memory effect. This class of shape memory alloys is triggered not only by changing temperature and stress, but also changing the magnetic field results in a relevant change in phase of the alloy. Here we present the design and fabrication process of a drug delivery mechanism for endoscopic capsule using shape memory alloys as the actuation mechanism.

DESIGN PRINCIPAL AND OPERATION

Shape memory alloys have the highest energy solidity which is in the order of $10\text{J}/\text{cm}^3$ for Ni-Ti alloys.¹⁴ Considering this, the Shape Memory effect appears particularly attractive for application with small dimensions, where large forces and displacements are required. With this in mind our proposed endoscopic capsule uses a spring made of shape memory alloy for achieving the actuation required to operate the drug delivery device. In the absence of the stimulus, i.e. in the "martensite phase", the SMA spring is in the compressed state. In the presence of the characteristic stimulus, i.e. in the "austenite phase", the spring is in extended state (Fig. 1). This change in length produces the desired actuation required for the drug delivery mechanism of the capsule. Apart from the spring the capsule consists of an outer shell made of polyethylene, a medicine pouch, a piston and a two-way micro valve (Fig. 2). The inclusion of the medicine pouch reduces the chances of leakage of the drug inside the capsule. The inner wall of the capsule surrounding the medicine pouch has a coating of PTFE, to reduce friction between the walls of the capsule and the pouch. The dimensions of the capsule along with its components are given in the Table 1. Before the application of the stimulus, the initial condition of the capsule is represented in Fig. 2. The principle behind the operation of the drug delivery mechanism is that when a characteristic stimulus is given to the shape memory alloy spring (say SMA spring "A"), it will begin to actuate and will expand. The expansion of the spring will push the piston forward, which in turn will exert force on the medicine pouch. The pressure inside the medicine pouch and the medicine will be pushed out of the medicine pouch via the two-way valve (Fig. 3). For

the spring to actuate and change its geometry, one has to train the SMA spring. Available training methods for the SMA spring are one-way training method and two-way training method. These two methods of applying shape memory effect in the SMA spring "A" have their impact, both on the design and operation of the capsule (see below).



Fig. 1: Different Phases of SMA

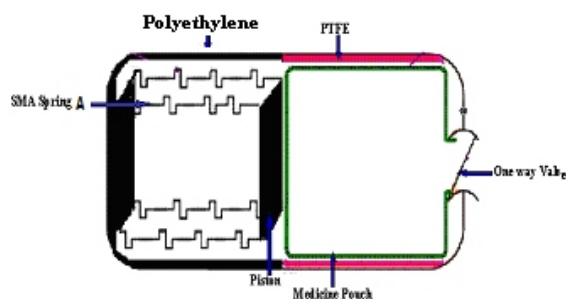


Fig. 2: Design of prototype before actuation

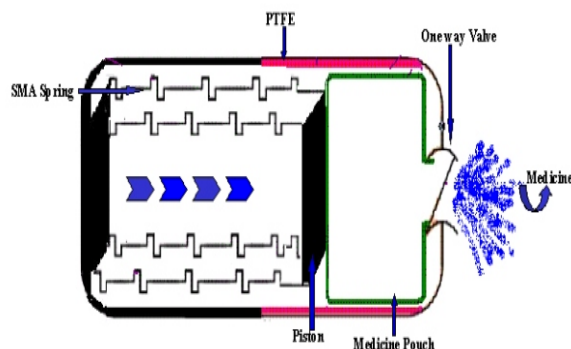


Fig. 3: Design of prototype after actuation

Table 1: Components and dimensions of capsule

Constituent	Material	Length
Outer Shell	Polyethylene	26 mm × 11 mm
Medicine Pouch	Latex	10 mm × 9.5 mm
Piston	Aluminum	1 mm × 9.5 mm
Actuator	SMA spring	Initial Length: 14.5 mm Outer Diameter: 8.64 mm Inner Diameter: 6.5 mm

SMA MICRO VALVE

The SMA micro valve used in the Capsule has the function and structure similar to the check valves available commercially. The structure of the micro valve consists of a SMA spring (say SMA spring "B") and a steel spring¹⁴ as given in Fig. 4. The micro valve is unidirectional having two-ports or two openings in its body, one port allowing the drug to enter in and the second port allows the drug to leave the valve.

The SMA spring "B" in the micro valve is essentially a small scale version of SMA spring "A" used in the drug delivery mechanism of the capsule. As mentioned before the SMA spring "A" used in the drug delivery mechanism can either be trained using a one-way method or a two-way method for imparting the shape memory effect. In this case, it is vital to understand that the two way method to impart shape memory effect in the SMA spring "B" is the only viable method hypothesized to be better for implementing the shape memory effect as it will be discussed later. Apart from the method used to train the two springs (SMA spring "A" & SMA spring "B"), the core actuation and functional principal of the SMA spring "B" used in two-way micro valve is the same as for the SMA spring "A" used for actuation purposes. Also, as both SMA spring "A" and SMA spring "B" shall be fabricated from the same material, therefore the characteristic stimulus is also the same.

The actuation mechanism of the SMA spring "B" used in the micro valve is shown in Fig. 4 and Fig. 5. When the characteristic stimulus is given to the SMA spring "B" inside the micro valve, the SMA spring actuates and expands and as a result it pushes the steel spring back. As a result of the expansion of the SMA spring "B" the channel in the micro valve is aligned with the two openings providing a pathway for the drug to flow out as shown in Fig. 5. When the stimulus is removed, the SMA spring "B" falls back to its "martensite" state, thus allowing for the steel spring to expand and as a result removing the pathway between the two openings.

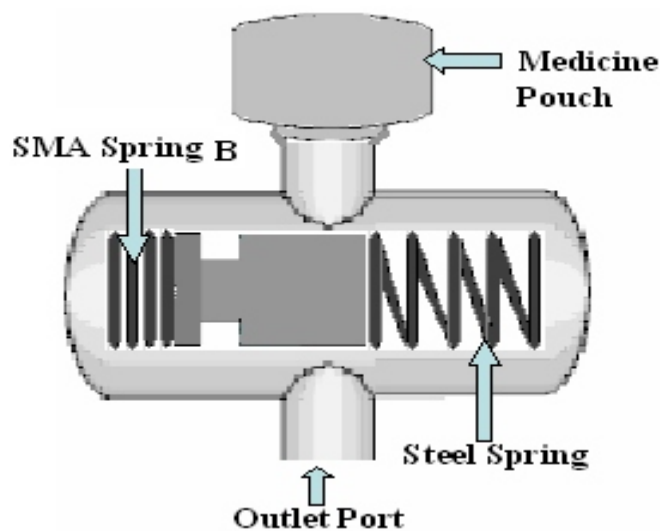


Fig. 4: State of micro valve before actuation

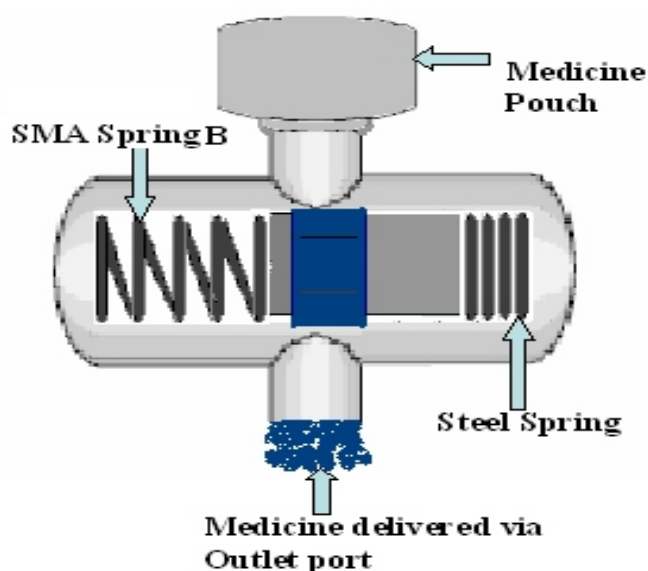


Fig. 5: State of micro valve after actuation

EXPERIMENTS

Nickel- Titanium (Nitinol) compression springs and rods were used; as they are readily available commercially. Nitinol is a "paramagnetic" thermal shape memory alloy whose characteristic actuation is achieved by applying thermal stimulus. As mentioned above, for the alloy to do a desired actuation, either one-way or two-way training has to be performed. In order to implement the shape memory effect in Nitinol, a set of experiments were performed. The apparatus, procedure and the results for the training are presented below.

ONE WAY SHAPE MEMORY TRAINING FOR NITINOL

In this training process the shape memory alloy only remembers one shape, at "austenite" phase and cooling the material will not cause it to revert back to "martensite" shape.¹⁵ Similarly, renewed heating of the material will have no effect either. The one-way shape memory effect is shown in detail in Fig. 6. The experimental procedure used to implement one-way shape memory effect in the Nickel-Titanium alloy was as follows:

1. Fill a beaker with 1 litre of water.
2. Place the beaker on the heating plate.
3. Hang the thermometer using the stand in the beaker.
4. Place the magnet with the rotating rod inside the beaker to ensure constant stirring of water.
5. Take the Nitinol (NiTi) and place it in the constraining structure. In our case, for the NiTi rod we used a stainless steel metal plate with two screws on it, parallel to each other and placed at a distance of 75 mm apart as shown in the Fig. 7. The NiTi rod was placed in between these screws and the screws were then tightened so as to constrain the rod in a straight position. For the Nitinol compression spring, we used two stainless steel plates, both parallel to each other at a distance of 36 mm apart as shown in Fig. 8. The spring was extended and was placed on top of the two metal plates. Heat the furnace to about 550 °C.
6. Place the constraining structure along with the Nitinol spring in the furnace and leave it for 15 minutes.
7. Prepare an oil bath (at room temperature) using the 3-litre container.
8. After 15 minutes, take the constraining structure out of the furnace (along with Nitinol) and place it in the oil bath, to allow it to cool down to room temperature.
9. Fill another container with cold water.
10. Unscrew the Nitinol from the constraining structure and place it in cold water.
11. Deform the Nitinol to the desired amount while it is in cold water.
12. Now using a pair of breaker-grozier pliers place the Nitinol in hot water.

Observe the alloy as it changes shape.

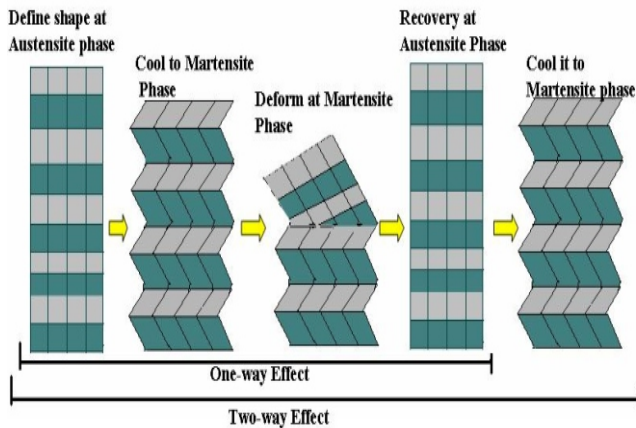


Fig. 6: Illustration of phase transitions [16]

TWO WAY SHAPE MEMORY TRAINING FOR NITINOL

In the two-way shape memory method, a shape memory alloy is trained to remember two different shapes at two different temperatures. That is, a shape memory alloy remembers a specific shape in "martensite" state and a different geometric shape in "austenite" state. So by stimulating the SMA from "martensite" phase to "austenite" phase or vice versa, causes the shape memory alloy to alternate between two different shapes. This process is depicted in Fig. 6. The two way shape memory method is a "reiterate" method. In order to implement the two-way shape memory method in "Nitinol" the following procedure can be followed.

1. Follow the one way training method up to step "11" as described previously.
2. Once the "Nitinol" is at the "martensite" temperature, deform the alloy to a specific shape, say "A".
3. Now stimulate the alloy so that it reaches its "austenite" state. Once the alloy reaches its "austenite" state it will attain the pre-defined furnace shape say "B".
4. Now again change the stimulus so that the alloy comes to its "martensite" state. While the alloy is in again "martensite" state, deform the alloy exactly to shape "A" as done in step 2.
5. After deformation to shape "A", again stimulate the alloy to "austenite" phase so that it recovers it pre-defined shape "B".
6. 20 -30 iteration of steps '4' and '5' will impart two-way memory in "Nitinol".



Fig. 7: SMA rod in a constraining structure

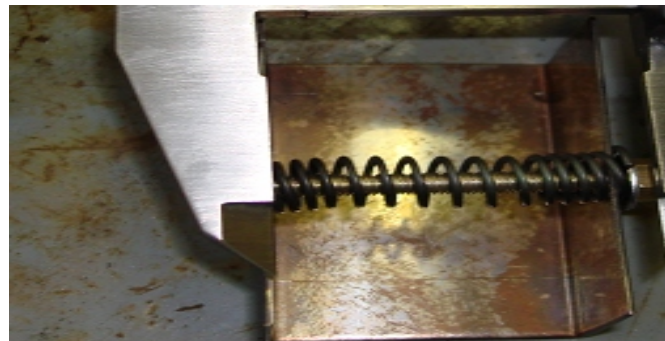


Fig. 8: SMA spring in a constraining structure

EXPERIMENTAL RESULTS OF SMA

Measurements and characteristics of SMA were observed and obtained during these experiments. Different structures like wire, rod and compression springs of "Nitinol" were trained using the one-way training method which is illustrated in Fig. 6. The point of interest in these experiments was to implement an extension of at least 10-11 mm in a Nitinol compression spring by using one way training. The experimental results are summarized in Table 2 and Fig. 9.

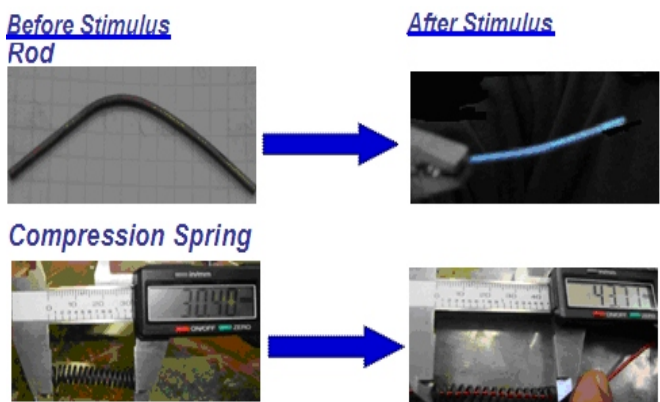


Fig. 9: Shape transitions of SMA

Table 2: Results from experiments performed on SMA

Nitinol Structure	Austensite temp °C	Martensite temp °C	Furnace temp °C	Room temp °C	Type of deformation applied in "martensite" phase	Final state of Nitinol at "austensite" phase
Wire	89	7	550	19	Straightening of wire	Wire bends at right angle from the middle
Rod	95	7	550	16	Bending the rod at right angle from the middle	Rod straightens up
Compression spring	82	7	550	19	Extending the spring to 38 mm	Spring shows compression and attains a length of 24.83 mm
Compression spring	82	7	550	19	Compressing the spring to 0.4 mm	Spring shows extension and attains a length of 43.71 mm

PROTOTYPE DRUG DELIVERY DEVICE

The prototype of the endoscopic capsule was fabricated using a one way trained thermal shape memory alloy (Ni-Ti) spring as an actuator to push against the latex medicine pouch. The summary of the dimensions of the prototype is given in Table 3. The valve's small dimensions resulted in its exclusion from the fabrication process of the prototype capsule due to manufacturing limitations. The outer shell of the prototype was fabricated from acrylic. Acrylic, being a transparent material, allowed the viewing of the actuation and working of the inner components of the capsule. The "front" and the "rear" ends of the capsule had openings of 5 mm and 3.6 mm respectively. As was stated previously, the inner components included a Ni-Ti spring with a convex piston resting over it. The latex pouch having a capacity of 0.5 ml (measured using micro pipette) was filled with water and placed on the face of the piston. The extension of the Ni-Ti spring was observed by connecting it with copper wires and running a current of 3.5 amperes through them. The wires were connected to the spring via the rear opening in the capsule. The temperature of Ni-Ti spring gradually increased and the spring started to

show actuation after 5 seconds of application of current. The Ni-Ti prototype capsule expelled on average 0.432 ml (measured with a micro pipette) of liquid via the front opening as shown in Figs. 10 & 11.

Table 3: Components and dimensions of prototype.

Constituent	Material	Dimensions
Outer Shell	Acrylic	Length: 61.30 mm Outer Diameter: 12.82 mm Inner Diameter: 10.79 mm
Medicine Pouch	Latex	12.09 mm × 10.87 mm
Piston	Hard Wood	11.23 mm × 9.62 mm
Actuator	Ni-Ti spring	Length: 22.5 mm Outer Diameter: 8.64 mm
Thermal Stimulus	Copper Wires	Length: 80.05 mm Diameter: 0.57 mm

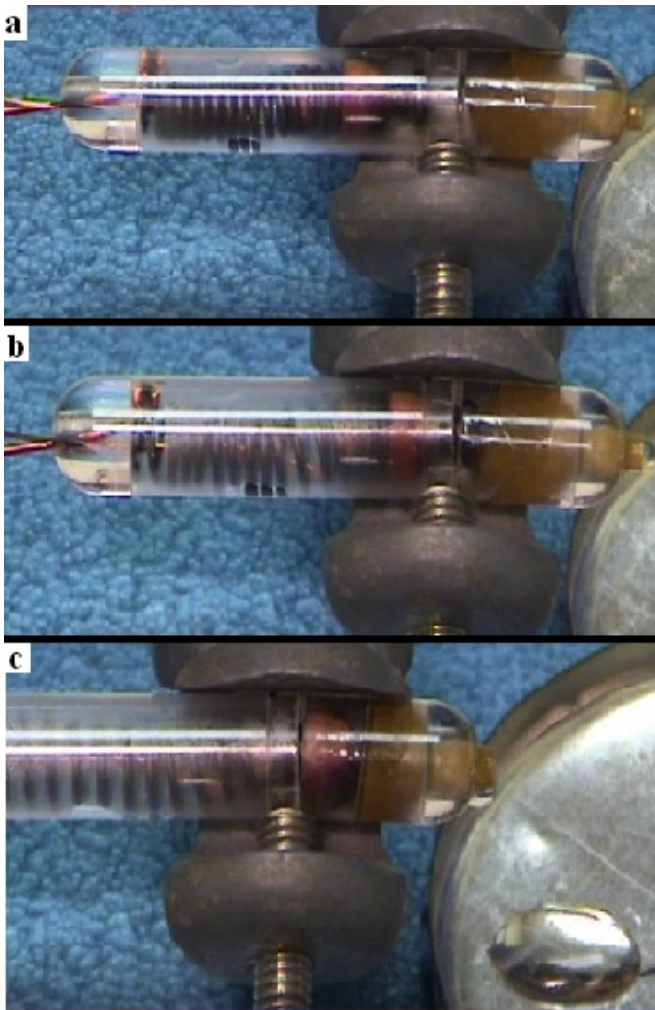


Fig. 10: Photographs depicting operation of the capsule

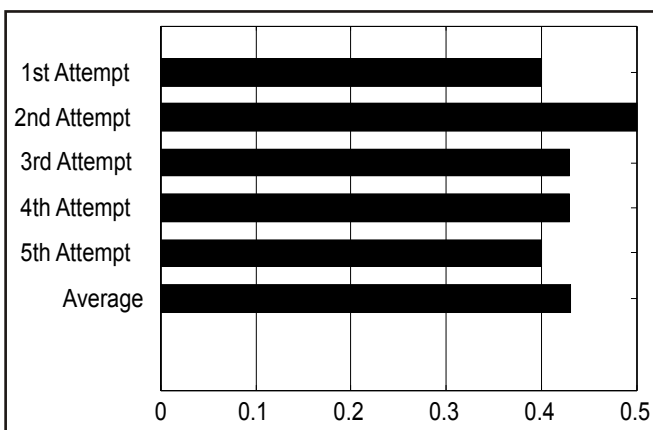


Fig. 11: Amount of liquid expelled by the capsule

PERFORMANCE CHARACTERISTICS

As mentioned previously, the TSMA spring can be considered the heart of the drug delivery system of

the Capsule. As a thermal shape memory alloy has been used in the prototype so the amount of expansion of the spring depends on the variation of temperature as shown in Fig. 12 (Graph 3). Before the start of the experiments the initial length of the TSMA spring was 22.5mm. After 5 seconds of application of current, TSMA showed an actuation of 0.5 mm as shown in Fig. 12 (Graph 4). At 87°C the TSMA spring showed an extension of 17.75 mm in 26 seconds as shown in Fig. 12 (Graphs 1 & 2). For most parts of the experiment it was noted that for every 2°C rise in temperature the TSMA spring showed an extension in the range of (0.5-0.75) mm. Also as thought, TSMA didn't show any noticeable increase in length when it reached its "austensite phase". Moreover the liquid expelled out by the capsule was in a constant range of (0.4-0.5 ml), with 0.4 ml being the least amount of liquid expelled out as depicted in Fig. 11. Table 4 shows a summary of the prototype device's performance characteristics.

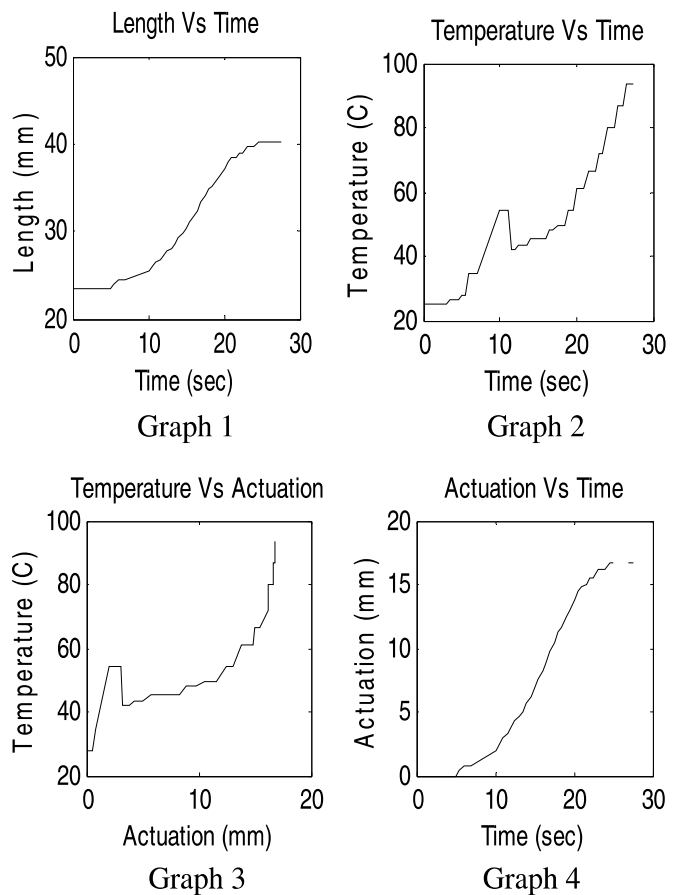


Fig. 12: Performance characteristics of the device

FURTHURENHANCEMENTS

The TSMA prototype was mainly intended for a single delivery of the same drug. However, there is a possibility that if there are multiple lesions at different locations in the digestive tract, a patient may be required to swallow several drug delivery capsules. The cost of the procedure will be higher and the process will be time consuming for both the patient and the physician. It will be far more economical to design the capsule in a way that allows multiple deliveries of the drug at different locations within the digestive tract. This can be done by applying the one-way method of training to the main actuation SMA spring "A" and performing the two-way training on the SMA spring "B" located inside the valve. Also, the characteristic stimulus should be applied for a shorter period of time than usual. The reactions of SMA spring "A" and SMA spring "B" upon receiving the short duration stimulus are described below:

1. Upon application of the stimulus, the one-way trained SMA spring "A" will start to extend. Because the stimulus is for a short duration, the spring will not extend to its full capacity. Consequently, when the stimulus is removed the spring will have covered certain amount of displacement in the forward direction. As the spring is one-way trained, it will not revert back to its "martensite" shape.
2. In the case of the two-way trained valve spring "B", the application of the stimulus for a short duration will actuate the spring, thus opening the valve. Removal of the stimulus will result in closing of the valve as spring "B" will revert

back to its "martensite" shape. During the short intervals of stimulus application, the SMA spring "A" will push against the medicine pouch, but as spring "A" is not fully extended only a portion of the drug will be released via the valve. Consequently, proper timed intervals will result in administration of the same drug at various locations inside the digestive tract. Fig. 13 depicts this concept in which the SMA spring "A" has progressively extended after multiple application of the stimulus.

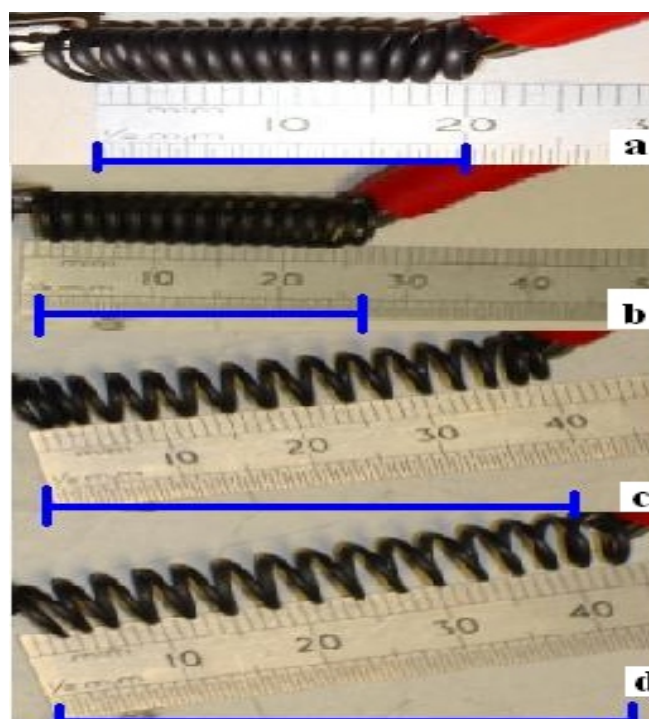


Fig. 13: Pictures depicting displacement length of SMA spring for use in multiple deliveries.

Table 4: Prototype performance characteristics

Initial Length "Li" of SMA Spring (mm)	Current (A)	Initial Time (sec)	Average Time to start of SMA actuation	Final Length "Lf" of SMA Spring	Displacement "Lf - Li" (mm)	Drug Capacity (ml)	Average Time "Ti" to start of drug release (sec)	Average Time "Tf" to complete drug release (sec)	Average Time to administer drug "Tf - Ti" (sec)	Average amount of drug delivered (ml)
22.5	3.5	0	6	34.5	12	0.5	17	33	16	0.432

CONCLUSION

The design, construction and testing of a laboratory prototype for a drug delivery device is in an endoscopic capsule for targeted delivery of

biomarker probes and/or drugs to conventionally inaccessible regions of the gastrointestinal tract. The dimensions of the proposed capsule (29mm x 11mm) are close to those of commercially available

capsules for imaging applications. The device is capable of delivering both multiple and single deliveries of the same drug. Shape memory alloys were used as the actuation mechanism for the drug delivery system. The design presented contained two shape memory alloy springs, which were trained specifically to achieve the desired actuation. It was further estimated that using springs fabricated from ferromagnetic shape memory alloys, more rapid actuation could possibly be achieved compared to the actuation obtained using springs made of thermal shape memory alloys. With further enhancements, the proposed drug delivery mechanism will be suitable for use in an endoscopic capsule for effectively administering biomarker probes to specific locations of the gastrointestinal tract.

Conflicts of Interest: None declared
Corresponding author email: drkhan49@hotmail.com
 Rec. Date: Mar 31, 2012 Accept Date: Nov 05, 2012

REFERENCES

- Waye JD, Rex DK, Williams CB. Colonoscopy: principles and practice. Malden;Massachusetts:Wiley Blackwell Inc; 2003.
- Mylonaki M, Fritscher-Ravens A, Swain P. Wireless capsule endoscopy: a comparison with push enteroscopy in patients with gastroscopy and colonoscopy negative gastrointestinal bleeding. *Gut* 2003;52:1122-6.
- Shah T, Aziz M, Vaithianathan T. Development of a tracking algorithm for an in-vivo RF capsule prototype. *Proceedings of ICECE 4th International Conference on Electrical & Computer Engineering*. 2006;173-6.
- Harm from endoscopy or colonoscopy. Bandolier Publishing Evidence Based Thinking about Health Care. Available from: www.medicine.ox.ac.uk/bandolier/booth/gi/endoharm.html.
- Tessaro I, Mangone C, Parkar I, Pawar V. Knowledge, barriers, and predictors of colorectal cancer screening in an appalachian church population. *Prev Chronic Dis* 2006;3:A123.
- Rosch T, Adler A, Pohl H, Wettschureck E, Koch M, Wiedenmann B, et al. A motor-driven single-use colonoscope controlled with a hand-held device: a feasibility study in volunteers. *Gastrointest Endosc* 2008;67:1139-46.
- Lee DW, Park JS, Park SH, Park JO, Yoon HS. MEMS-based modular actuator for capsular endoscope applications. *Microelectronic Engineering* 2007;84:1278-81.
- Butler RN. Biochemical tests of small intestinal function. In: Retnaikie RN, editor. *Small bowel disorders*. London:Arnold;2000.p. 222-30.
- Brown GJ, Saunders BP. Advances in colonic imaging: technical improvements in colonoscopy. *Eur J Gastroenterol Hepatol* 2005;17:785-92.
- Rajan R, Aziz M, Vaithianathan T. An electrically controlled micromachined drug delivery device employing two silicon wafers. *Prog Biomed Imaging* 2006;6416:64170.
- Vasina M, Solc F, Hoder K. Shape memory alloysunconventional actuators. *IEEE International Conference on Industrial Technology*. 2003;1:190-3.
- Srinivasan AV, McFarland DM. *Smart structures: analysis and design*. London: Cambridge University Press; 2001.p. 25-8.
- Heczko O, Ullakko K. Effect of temperature on magnetic properties of Ni-Mn-Ga magnetic shape memory (MSM) alloys. *IEEE Transactions on Magnetics* 2001;37:2672-4.
- Kohl AM. *Shape memory microactuators*. Springer; 2004.p. 96-104, 160-162.
- Otsuka K, Ren X. Physical metallurgy of Ti-Ni based shape memory alloys. *Prog Mater Sci* 2005;50:511-678.