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A novel remote controlled capsule for site-specific drug delivery in human GI tract

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ABSTRACT

Remote controlled capsule (RCC) has been extensively used in the field of site-specific drug delivery. It is a potent tool to study the regional drug absorption of the gastrointestinal (GI) tract that provides pharmaceutical scientists with significant pharmacokinetics data for oral drug formulation development. In present investigations, a patented novel RCC has been devised based on micro-electronic mechanical system (MEMS) technology. Micro-thrusters were for the first time exploited as drug release actuators of RCCs. As the micro-thruster is ignited by a radio frequency (RF) signal, the thrust force generated by the propellants pushes the piston forward and leads to a rapid and complete expulsion of therapeutic agents from the capsule. The micro-thruster merely consumes 120 mW for ignition and the duration time of drug release is decreased to less than 1 s. The feasibility of the novel RCC was evaluated through animal experiments in beagles using aminophylline as the model drug. The novel RCC developed is a promising alternative for site-specific drug delivery in human GI tract.

1. Introduction

Over recent years, the advance in combinatorial chemistry, proteomics and genomics encourages the rapid emergence of challenging new molecular entities (NMEs). Most of these NMEs are potential drug candidates, whereas few of them possess ideal biopharmaceutical properties for oral administration. This presents great challenges for pharmaceutical scientists in terms of both candidate selection and optimization of the subsequent development strategy. To date regional drug absorption (RDA) studies using RCC have been widely acknowledged as a non-invasive means to acquire significant pharmacokinetics data for oral drug formulation development (Rouge et al., 1996; Gardner et al., 1997; Parr et al., 1999; Wilding, 2000; Wilding et al., 2000; Wilding and Prior, 2003).

Marked improvements have been made during the exploration of the RCC, as stated in previous studies (Wilding et al., 2000; Wilding and Prior, 2003). Considerable parameters are employed to evaluate a RCC, parameters as reliability, the dimension of the capsule, the volume of the drug reservoir, the duration time of drug release, the proportion of residual volume, etc. Generally, the drug delivery achieved by RCC for RDA studies should be fast and complete.

The high-frequency (HF) capsule (Battelle-Institute V, Frankfurt am Main, Germany), for instance, encapsulates a latex balloon as the drug reservoir. A needle is activated on demand using a HF generator to pierce the depot, eventually resulting in the drainage of drug contents. The capsule is unfortunately more suitable for liquid than for powder or particulate formulations. The Gastrotarget telemetric capsule (Gatrotarget Corporation, Tonawanda, NY, USA), as is the Telemetric capsule (INSERM U61, Strasbourg Cedex, France), has a more complex mode of operation to trigger medicament releasing than does the HF capsule (Hugemann et al., 1984; Lambert et al., 1991; Schentag and D'Andrea, 1994; Wilding et al., 2000; Wilding and Prior, 2003).

The InteliSite capsule, developed by Innovative Devices (Raleigh, NC, USA), has a uniquely shaped body with one or more apertures in the circumferential wall, a sleeve valve rotatablely mounted inside of which is accordingly drilled with apertures (Casper et al., 1992; Gardner et al., 1997; Pithavala et al., 1998; Cook et al., 1998; Parr et al., 1999; Mummaneni et al., 1999; Wilding et al., 2000; Clear et al., 2001). Shape memory alloy wires segments responsive to heat are used to rotate the inner sleeve to align slots of it with those of the outer, and thus the drug sealed in the inner sleeve was exposed to GI fluids for subsequent passive release. The velocity of such release

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manner, especially to the distal colon, would be somewhat slow were solid formulations loaded in the reservoir (Clear et al., 2001). In addition it typically takes over 2 min to heat the shape memory alloy wires, risking the possibility of missing the defined location in the GI tract (Pithavala et al., 1998; Parr et al., 1999; Clear et al., 2001). The new generation InteliSite device (InteliSite Companion) encounters the identical issue though the deformation of two shape memory alloy wire clips to free the spring is decreased to 2 min (McGirr et al., 2009).

Enterion capsule (Phaeton Research, Nottingham, UK) is currently the leading RCC used in RDA studies (Wilding et al., 2000, 2004; Charles et al., 2003). The ejection of the drug from the capsule rests upon a piston that is driven by coils of spring to push the drug out of the reservoir. The special design of this capsule has the advantage of quick and complete delivery of both liquid and particulate formulations to any location of the entire GI tract, yet from the perspective of aerodynamics and aerostatics it suffers some deficiencies in the active delivery mechanism. As the piston is gradually pushed forward by the actuation spring, the internal pressure within the compartment behind the piston will fall accordingly. The negative pressure within the compartment increases the potential for drug reflux, especially for solution formulations.

Gas producing cell has been otherwise employed as a propulsion apparatus in capsule-style drug delivery systems (Gröning et al., 2007, 2008). It is the hydrogen gas generated by the cell that pushes the piston against the drug reservoir until the therapeutic agents are entirely emptied. Although the drug-release rate can be regulated by modifying a resistor to control gas producing process, the drug release process still lasts up to or over 10 min (Gröning et al., 2008).

The main objective of this paper is to develop a novel activation mechanism for the novel RCC dependent on micro-electronic mechanical system (MEMS) technology. It is the micro-thruster principally applied in the spectrum of micro-spacecraft propulsion that activates the drug release, an avenue first used in RCC (Xitian and Hongying, 2006). The proprietary drug release design consists of a micro-thruster, a sliding protective shell and a piston. Once the thruster is ignited by an external RF signal, the thrust force generated by propellants pushes the piston forward with great acceleration and expels entirely the drug out of the dosing reservoir, overcoming to a large degree the limitation of drug reflux. In vitro experiments and tests on beagles demonstrated that the novel system could be a promising new alternative for non-invasive RDA studies.

2. Materials and methods

2.1. Development of the novel RCC with a micro-thruster

The novel RCC developed in this study is 30 mm long and 10.4 mm in diameter that consists of a shell, piston/embedded magnetic marker, telecontrol unit, drug release actuator, silicone O-ring and button cells. The sectional view of the novel RCC is shown in Fig. 1. The shell is made of biocompatible polycarbonate (MAKROLON® 2458, Bayer, Germany), which meets the requirements of FDA-modified ISO 10993-1 and USP Class VI testing. Two shells are glued together using medical device adhesive (Loctite® 4014, Henkel, USA). The piston and the O-ring seal are both made of medical grade silicone elastomer (SILASTIC® MDX4-4210, Dow Corning Chemical Co., USA).

The compartment between the piston and the silicone O-ring seal serves as the drug reservoir into which up to 0.6 ml of either powder or liquid formulation can be filled. The drug reservoir is separated from the drug release actuator by a piston, stuffed with drug contents through a circular opening, and ultimately closed by a silicone O-ring seal.

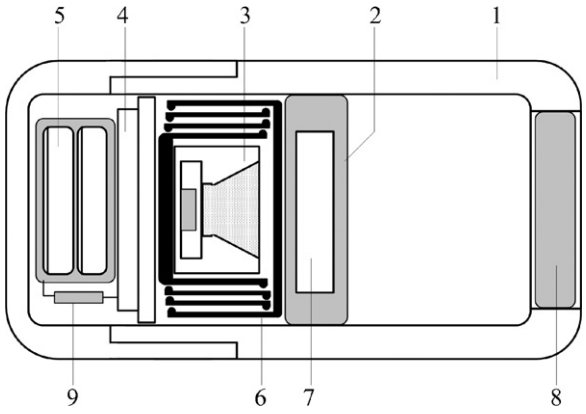

Fig. 1. Structure diagram of the novel RCC with a micro-thruster. (1) Shell, (2) piston, (3) micro-thruster, (4) telecontrol circuit, (5) button cells, (6) sliding protective shell, (7) magnetic marker, (8) silicone seal, and (9) magnetic switch.

To localize the capsule after administration, a tiny magnetic marker is embedded in the piston. This permits real-time monitor of the capsule location using a wearable magnetic locating and tracking system (Xudong et al., 2008). The radio-opaque button cells make the X-ray imaging also accessible in visualizing the navigation of the capsule in vivo.

As the novel capsule arrives at the predetermined location of the GI tract the dosing procedure is initialized by applying a 330 MHZ RF signal emitted by a telecontrol device external to the body. The RF signal is received by a miniaturized telecontrol circuit assembled in the capsule and in turn fed to the drug release actuator integrated with a PCB antenna and a micro radio frequency relay module. This allows the button cells sealed in the capsule to power the micro-thruster. Substances from the chamber are forced off through the ignition of the propellant in the micro-thruster.

To strengthen the security the micro-thruster is placed in a sliding protective shell that is fabricated by four metallic layers. The innermost one is a tumbler-shaped container with the lip welded by a small metal ring and the bottom directly secured to the floor of the thruster. The micro-thruster was hard-wired to the telecontrol circuit through holes of the bottom. The middle two, layer by layer, are tube-like both with a pair of metal rings welded respectively at the end. The outermost one is same shaped as the first except for its dimension and the opening of which a metal ring is welded at the inner edge. It approximately contacts with the capsule's inner wall and inversely shields all the other layers.

Not until the capsule is activated did the four metallic layers start to unfold, forming a compact sleeve (Fig. 1). Two adjacent layers, preceded by the activation of the capsule, constitute a motion unit and the sliding shell moves in a series manner. As the thrust is applied on the bottom of the outermost layer, it slides forward and involves the nested layer in the same course once the meeting of two rings. Such movement continues layer by layer until the piston is restrained by the dosing orifice. Consequently each layer leaves its original place and the entire capsule contents are driven out of the chamber. Fig. 2 is the schematic diagram of the operational principle of the sliding protective shell as the micro-thruster is ignited.

2.2. Micro-thruster fabrication

The micro-thruster is the critical component of the novel RCC. The micro-thruster is comprised of a combustion chamber filled with propellants, a micro-igniter, an electronic circuit board and bonding wires. Fig. 3 gives a schematic diagram of a single thruster and a photograph of the micro-fabricated igniter. Since the thruster

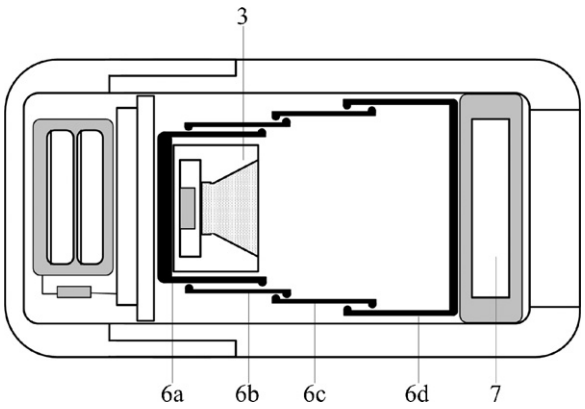

Fig. 2. Schematic diagram of the operational principle of the sliding protective shell when the micro-thruster was ignited. (3) Micro-thruster, (6a) the first layer, (6b) the second layer, (6c) the third layer, (6d) the fourth layer, (7) piston with magnetic marker.

contains no moving parts such as pumps, fuel lines or valves, the entire system is fully integrated, thus achieving great space efficiency and reliability. The wall of combustion chamber is made of high purity copper (Cu) by precise metalworking and the hollow area of it is much as a small basin with height 3.5 mm, inclination of the side 12°, the diameter of the large opening 6 mm and the small opening 4 mm. The base of the cavity is sealed by an electronic circuit board on which a micro-igniter is centrally positioned and connected with bonding wires.

The micro-igniter or micro-heater was fabricated through silicon micromachining process. Low-pressure chemical vapor deposition (LPCVD) was used to dope thin-film silicone compounds onto the substrate. Two metal layers were subsequently sputtered on the former coatings and Ti–W thin-film technique was particularly employed to meet the requirements of device specification. The lead and the resistance regions were then photolithographically patterned in a given order. Finally, the wafer was grinded to 100 μm thick and the single micro-igniter 500 μm long and 100 μm in width is shaped by IC scribing process.

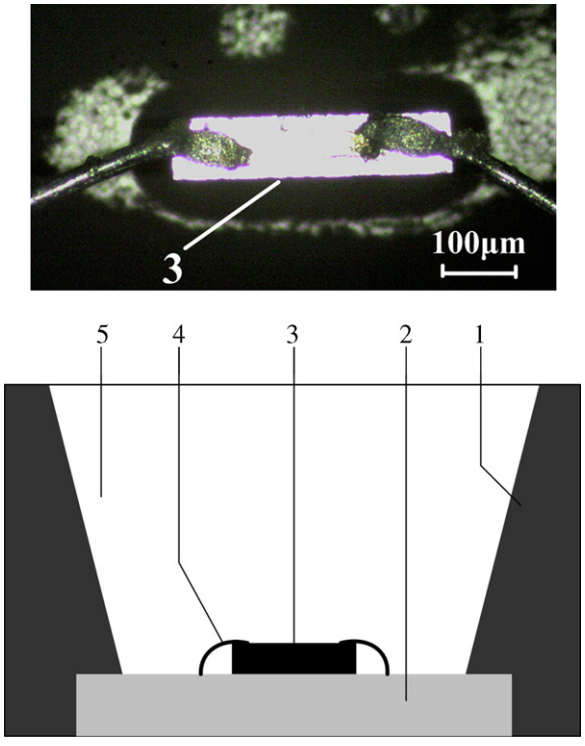

Fig. 3. Photography of the novel RCC with a micro-thruster.

The thruster was assembled after the sequential fabrication process was completed. First, the micro-igniter was bonded to the electronic circuit board using insulating adhesive and was connected to it by ultrasonic bonding process with Ø30 μm silicon–aluminum wires. The electronic circuit board was hermetically sealed on the bottom of the combustion chamber using medical device adhesive (Loctite® 4014, Henkel, USA). Second, precise amount of the propellant, black mixed powder in this study (74.6% potassium nitrate; 11.9% sulfur; 13.5% charcoal), was deposited into the combustion chamber. The mass of the propellant was accurately calculated in terms of parameters as the friction of the sliding protective shell, the piston and the O-ring seal, etc. and in turn optimized to 25–30 mg. The propellant filling work was undertaken in a fume hood and due to safety concerns the operator worn protective spectacles. The power consumption of the micro-thruster to ignite the propellant declined to 120 mW thanks to the above-mentioned MEMS technology.

2.3. In vitro release from the novel capsule

In vitro experiments were carried out to characterize its feasibility and practicability. Normal saline, as the release solution, was prepared in a rectangular jar (length 40 cm, width 20 cm, depth 20 cm). Sixteen identical capsules were divided into two groups, one having aminophylline solution (100 mg dissolved in 0.5 ml water) filled into the reservoir, and the other having 100 mg aminophylline powder (purity 99.7%, the department of pharmacy, Southwest Hospital, Chongqing, China) added. Each capsule was sealed by a silicone O-ring seal and enclosed in a metallic box. The capsule was one by one immersed in the normal saline. The hand-held telecontrol device was 30 cm away from the capsule and a digital stop watch (DM3-008, Diamond, China) was used to measure the duration time of drug release (T_D, s), i.e., the time between the capsule starts activation and the piston is stopped by the dosing orifice.

The capsule was first taken out from the solution immediately after release and then immersed in a Bunsen beaker filled with 50 ml distilled water. After stirring 2 ml sample was taken from the beaker and the theophylline concentration of it was determined by TDx analyzer (Abbott™ Laboratories, Dallas, USA).

2.4. In vivo study

Preliminary in vivo experiments were carried out in fasted beagles, which was in accordance to all the ethical considerations and the regulatory issues related to animal experiments. Six conscious fasted beagles were comfortably restrained in a standing position and each administered with a novel RCC containing 100 mg aminophylline powder. The novel RCC was immediately delivered to the throat of the beagle with 100 ml distilled water and 10 g barium meal given to stimulate the beagle to swallow.

The location of the novel capsule in the beagle's intestine was followed by a low-dose fluoroscopy (Iconos R200, Siemens, Germany) instead of our magnetic locating and tracking system that was initially designed for volunteers (Xudong et al., 2008). The barium meal fed to beagles made possible the localization of the novel capsule in the intestine by X-ray. The beagle was X-rayed every 30 min until the novel capsule was detected in the GI region of interest. 2 ml blood sample was subsequently taken to check for any leakage or contamination. After that the external telecontrol device was held close to the beagle and switched on for 10 s. The beagle was again X-rayed to ensure if the drug succeeded to be released into the alimentary tract immediately after the novel capsule was activated.

Fig. 4. Schematic diagram of the micro-thruster and a photograph of the micro-fabricated igniter. (1) Combustion chamber; (2) electronic circuit board, (3) micro-igniter, (4) bonding wire, and (5) propellant.

After the confirmation of drug release blood samples were taken at 0, 0.33, 0.67, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, 10.0 and 12.0 h. They were centrifuged at 3000 r/min for 10 min and the plasma samples were transferred to EP tubes and kept frozen at −20 °C for analysis. The concentration of theophylline in plasma samples was detected by a TDx analysis based on fluorescence polarization immunoassay technology.

3. Results and discussions

The novel RCC developed is shown in Fig. 4. The size of the novel RCC is similar to or smaller than Enterion and InteliSite. It would therefore not be expected to have any difficulties for ingestion. The main capsule body is made from polycarbonate which is safe for oral administration and should also have better compatibility to loaded drug materials and most formulation excipients compared with other devices. The novel activation mechanism of the RCC that leads to a positive pressure within the compartment behind the piston could effectively eliminate drug reflux during activation process.

In the in vitro study, the novel capsule successfully delivered aminophylline solution and powder formulation into the normal saline on all 16 occasions. As show in Table 1, the mean T_D of the solution formulation released into the jar is 0.63 ± 0.04 s and that of the powder is 0.70 ± 0.04 s. In addition the mean percentage of the residual volume in the capsule is 5.7 ± 0.8% for the powder formulation, in stark contrast to that for the solution formulation which is 0.1 ± 0.02%.

Table 1
Duration time of drug release and percentage of the residual volume in vitro experiments.

Subject	Solution formulation		Powder formulation	
	T_D (S)[a]	V_R (%)[b]	T_D (S)	V_R (%)
1	0.66	0.11	0.78	6.4
2	0.67	0.09	0.72	4.8
3	0.65	0.10	0.68	5.7
4	0.56	0.08	0.75	4.6
5	0.68	0.12	0.7	5.3
6	0.62	0.09	0.66	5.7
7	0.58	0.07	0.67	6.6
8	0.64	0.10	0.69	6.4
Mean	0.63	0.095	0.70	5.69
s.d.	0.04	0.02	0.04	0.75

[a] T_D (S): duration time of drug release.
[b] V_R (%): percentage of the residual volume.

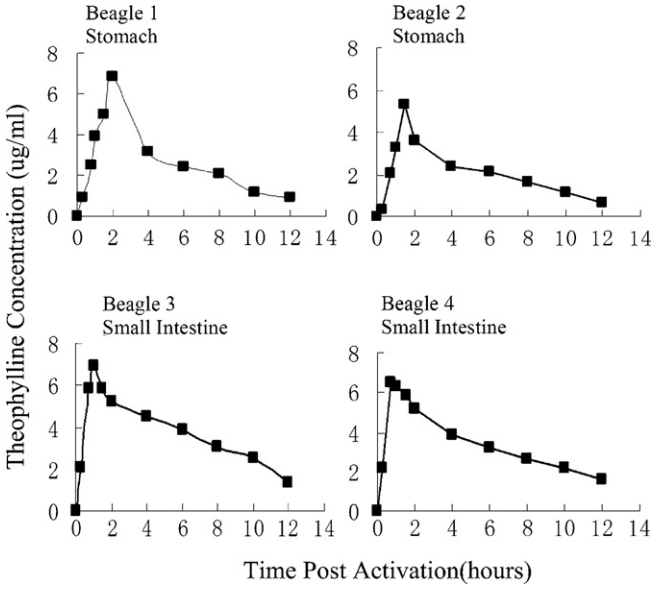

Fig. 5. Individual serum concentration profiles following oral administration of aminophylline powder (100 mg) in the novel RCC to fasted beagles.

In the in vivo study, the novel RCC successfully operated in four beagles of which the individual theophylline plasma concentration curves is depicted in Fig. 5. The model compound was first delivered to the stomach (Fig. 5(a) and (b)) and then to the small bowel (Fig. 5(c) and (d)). Two novel RCCs observed by X-ray failed to open the dosing cap and in vitro activation of them was as well futile after they were recovered. The failed were then disassembled and overhauled. It was found that the malfunction of micro-thruster was caused by inappropriate assembly. The theophylline plasma levels of samples taken before activation confirmed that there was no pre-activation leaking of the aminophylline. All the capsules after dosing were retrieved between 28 and 48 h and the GI tracts of beagles bore no sign of abnormity. In the capsule that operated properly the piston was observed to be attached to entry of the dose orifice, which indicated that the drug release was complete in vivo.

The novel activation mechanism of the RCC is feasible in both vitro and vivo studies, although further optimization of the device assembly process is necessary to reduce the failure rate in device performance. The future research on this novel device will also focus on the reduction of power consumption with resort to the state-of-the-art MEMS technology. The volume of the drug reservoir should be increased as to meet the clinical practice in that 0.6 ml does not suffice to study regional drug absorptions of all the drug candidates. For the concern of patient safety the dosage of the propellants should be precisely calculated and new energy sources possessing better bio-security will be preferred.

4. Conclusions

In this study a novel RCC was developed based on MEMS technology and the micro-thruster constituted for the first time the actuation assembly. Upon the receipt of a triggering signal the thruster was set in motion and generated by the combustion of propellants the pushing force against the drug reservoir. The electrical power to ignite the micro-thruster was merely 120 mW and the duration of drug release was decreased to less than 1 s.

The novel RCC was shown to be both well tolerated and safe to use in normal beagle dogs. The circuits and the micro-thruster assembly worked reliably, yet some techniques in manufacturing the capsule were necessary to be improved. The results of in vitro experiment and preliminary beagle study demonstrated that the

novel activation mechanism has been successfully applied in the RCC for site-specific drug delivery in the GI tract.

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