

[Chem. Pharm. Bull.]
36(4)1581—1584(1988)

New Externally Controlled Drug Infusion Pump

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(Received September 21, 1987)

An externally controlled infusion pump has been developed to deliver drug solution with a constant rate outflow. The prototype consisted of basically two units, the drug container and the external control unit. The container has two main functions: (1) drug storage and (2) drug supply. The driving force was derived from the external control unit and was conducted magnetically to the container. The external unit has basically two functions: (1) producing the driving force and (2) controlling the force. Using a popular laboratory timer as an external control unit, a prototype was built. The quality of the prototype was tested in an *in vitro* drug liberation experiment. As a drug solution, five ml of 5% 5-fluorouracil (5-FU) solution was introduced into the drug chamber, and the external control unit was set to rotate once an hour at the distance of 2.5 cm from the chamber. Just after the operation of the external unit, the outflow rate of 5-FU solution from the chamber was monitored for 60 min at 2-min intervals. After three experiments on different days, this system was confirmed to work well and the outflow rate was reproducible and showed high accuracy.

Keywords—drug delivery; infusion pump; externally controlled; magnetism; anticancer drug therapy

Introduction

As an approach to the delivery of drug molecules to their target organ, many investigators have been studying infusion pumps. The pumps are classified mainly into three categories according to their functions, namely (1) externally portable devices,^{1,2)} (2) implantable devices³⁻⁶⁾ and (3) implantable ones with a specific sensor.⁷⁻⁹⁾ The externally portable devices may be useful for patients with severe continuous pain²⁾ and with diabetes. On the other hand, the implantable devices have achieved excellent clinical results in the field of anticancer chemotherapy.³⁾ The characteristic of these high-technology implantable infusion device is that they have their own driving sources such as an electro-osmotic pump or a vapor-pressure pump. However, controlled drug delivery at variable rates has not been possible so far. To provide the system itself with a controllable driving unit would be complicated, with a consequent risk of failure. Therefore, we have tried to develop a prototype of an implantable infusion device in which the outflow rate of drug solution is easily adjustable externally, and the quality of the prototype was evaluated in an *in vitro* drug liberation study.

Materials and Methods

A schematic illustration of our prototype is shown in Fig. 1. The system is basically composed of two units. One is the container and the other is the external driving control unit. The rigid container measuring 10 × 2.8 × 6 cm

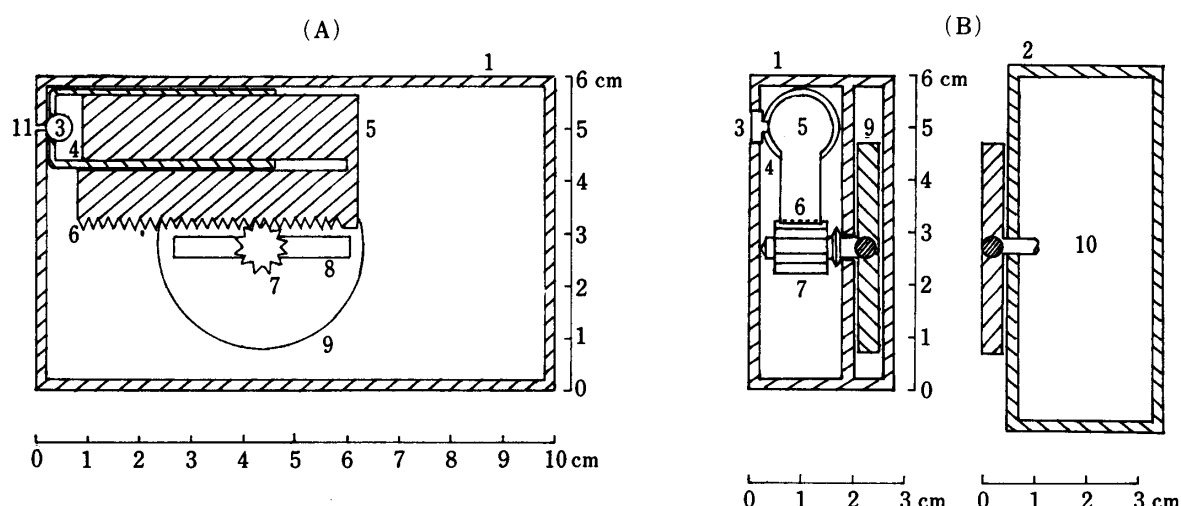


Fig. 1. Schematic Illustration of the Prototype of the Externally Controlled Implantable Drug Infusion Pump, Represented as Perspective Drawings from the Upper Side (A) and from the Right-Hand Side (B)

1, internal unit; 2, external unit; 3, injection port; 4, drug chamber; 5, plunger; 6, rack; 7, pinion; 8, magnet; 9, rotary disc; 10, timer; 11, outlet.

houses the (1) injection port, (2) drug chamber to which a plunger is closely attached, and (3) rack and pinion. The injection port has a septum which prevents the introduced drug solution from being washed away. The drug chamber (i.d. 1.2 cm, o.d. 1.5 cm) is made of glass in this system. However, a ceramic chamber could be substituted. The plunger (5 cm length) has a rack just outside the drug chamber, and this rack (made of plastic) is 5.4 cm in length and has 25 crowns. A pinion delivers the driving force to the plunger by converting a rotatory motion to a rectilinear motion. The drug chamber can contain at maximum 5 ml of drug solution. If the system needs a larger volume of the drug solution, one more chamber can be introduced inside the container symmetrically. The pinion has a diameter of 1 cm and has 12 crowns, being connected to a plastic disc having a diameter of 4 cm. This plastic disc contains a 300 G magnetic bar, 3.4 cm in length. The driving control unit has a 3000 G magnet made of samarium-cobalt, and generates a rotatory motion.

Results and Discussion

Five milliliters of 5% 5-fluorouracil (5-FU) solution was introduced through the injection port into the chamber of the prototype. As the experiment performed in this preliminary study was a *in vitro* one, the container was mechanically fixed to a laboratory stand. The driving control unit was also fixed to a laboratory stand and was set opposite the container. Figure 2 is a photographic representation of this experimental set-up. The space between these two units was determined by measuring the distance between the two magnets, and was varied from 0.5 to 3.0 cm in this experiment. To build a complete, well-controlled driving unit, a great deal of development expenditure would be needed. However, this study was a preliminary one to ascertain whether our prototype can liberate drug solution with a constant rate of outflow by means of an externally derived driving force. Therefore, we applied a mini laboratory timer produced by Citizen Corp. (Tokyo, Japan). This timer has a disc (4 cm diameter) on its surface and the disc rotates once an hour. A samarium-cobalt magnet was attached to the surface of the disc with an adhesive. At first, the distance between the two units was set to be 2 cm. After the driving control unit had been set to rotate once an hour, the outflow of the 5-FU solution from the container was collected in microcentrifuge tubes for each 2 min interval outlet over 60 min. The volumes of solution were determined gravimetrically. The experiment was performed three times on different days. Therefore, the result is represented as the mean outflow rate for each 2 min interval as shown in Fig. 3. By multiplying the concentration (50 mg/ml) by the measured volume, we can calculate the delivery rate of 5-

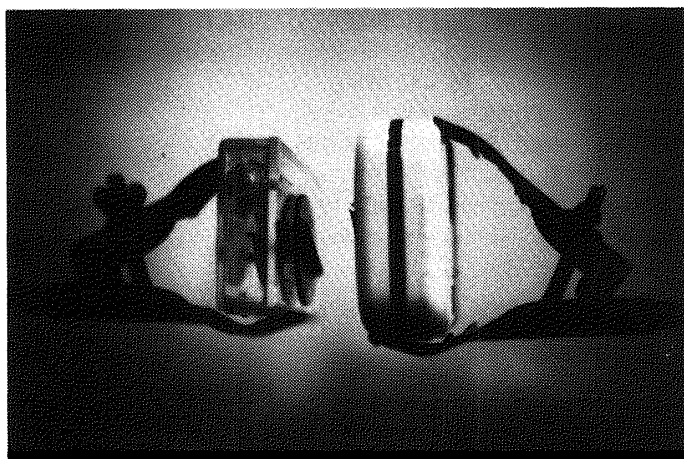


Fig. 2. Photographic Representation of the Experimental Set-Up Using the Prototype Infusion Pump

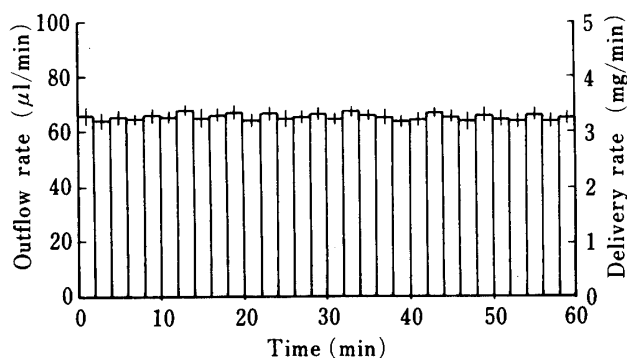


Fig. 3. The Outflow Rate of 5-FU Solution or Delivery Rate of 5-FU vs. Time Plot after Initiation of Rotation of the External Control Unit for 60 min

As the external control unit, a popular laboratory timer was used. The disc attached to the surface of the timer rotates once an hour.

FU. The scale on the right-hand side of Fig. 3 shows the delivery rate of 5-FU, mg/min, with the infusion pump. The outflow rate was well controlled and the coefficients of variation were less than 5% in each sampling interval. This result was obtained with the 2-cm distance between the two units. The experiment was also performed with distances of 0.5 to 3.0 cm in steps of 0.5 cm. When the distance was less than 1.5 cm, the magnetism was so strong that the system did not work well. In contrast, when the distance was longer than 3.0 cm, the magnetism became too weak, and well-controlled outflow rates were not obtained. Within the range of distance from 1.5 to 2.5 cm, this system worked efficiently. However, as this experiment was a preliminary one, we did not change the number of crowns on the rack or on the pinion. As the number of crowns is increased, the system should work more smoothly and we should be able to obtain better controlled outflow rates of 5-FU solution. The number of crowns is related to the rotation of the pinion, and if we double the number of the crowns, the outflow rate of the 5-FU solution would decrease to a half during one rotation of the disc. By adjusting the external control unit to rotate twice an hour, the same outflow rate would be obtained.

In this manner, the outflow rate of 5-FU solution is dependent on the number of crowns both on the rack and on the pinion, as well as the rotatory speed of the external control unit. Though this study was a preliminary one and the quality of this new drug infusion pump was evaluated only in an *in vitro* experiment, a constant outflow rate of the drug solution was obtained with rather high accuracy. The results justify further studies, including *in vivo* animal experiments.

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