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Computer-controlled release of metoprolol from capsules

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Summary

The present paper describes the development of a capsule-like model dosage form where the rate of release of a drug can be varied under the control of a computer. The capsules contain a simple electrical circuit with its own power supply. The circuit is switched on using a magnetic remote-controlled microswitch. Electrolytic breakdown of water is induced at two steel electrodes. The resulting gas pressure moves a piston which pushes a solution of drug out of a reservoir. A computer controls the release from the capsule according to a given program in a wireless manner via the magnetic field of an electromagnet. Capsules have also been developed with an external power supply. Investigations of the release of metoprolol solutions show that by varying the length of the switching on and pause intervals, 80 mg metoprolol can be released within a few minutes or the process can be prolonged, if desired, over several hours. A pulsed release at intervals of 2 h was achieved.

Introduction

With the dosage forms such as tablets or capsules used today, neither the physician nor the patient can actively influence the release of the drug either before or after ingestion. It is also impossible to tailor release for a particular patient. However, for future application of drugs, the ability to achieve a controlled variation in the release of drug substances from dosage forms would be highly desirable. The rate of release could be governed, for example, by the plasma level, the concentration at the site of action, metabolism data, physiological parameters, subjective assessment of therapeutic effect, diurnal variations in the requirement for the drug, or the data of a treatment schedule. With the current dosage forms, it is not possible to use sensing and control circuits, e.g., bio- or chemosensors, to control release.

Even with the existing therapeutic systems, such as osmotic pumps (Theeuwes, 1975), release cannot be varied once the dosage form has been taken. The aim of the present paper, which is linked to earlier work on the development of capsules with microelectronic circuits that release drugs electrophoretically (Gröning et al., 1991, 1992), is to investigate the use of other control principles. As in the previous studies, the new dosage forms use electrical energy to power the switching and control circuits. They were designed to control release by utilizing the pressure

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of gases resulting from the electrolytic breakdown of water at electrodes to expel a solution or suspension of a drug from a reservoir. This control principle has never been used before in tablets or capsules, although the electrolytic breakdown of hydrazine or of water has previously been employed by other workers in application systems for the administration of drugs by injection syringes (Ariel, 1965; Yamamotu et al., 1985).

Materials and Methods

Materials

Substances used were as follows: metoprolol tartrate (Ciba-Geigy, Basle, Switzerland); agar-agar, Pharm. Eur. (Caelo, Hilden, Germany), polysorbate 40, Pharm. Eur. (Atlas Chemie, Essen, Germany), and sodium chloride, Pharm. Eur. (Merck, Darmstadt, Germany).

Preparation of the application forms

The model capsule with an internal power supply consists of a 25 mm long section of plastic tubing (Plexiglass tubing, external diameter 7 mm, internal diameter 5 mm, Röhm, Darmstadt, Germany), which is drilled at one end to give an internal diameter of 6 mm for holding two miniature batteries each of 1.59 V (1.5 V, 5 mA h, 1.25 mm × 5.8 mm ∅ type 317, Renata, Itlingen, Switzerland). The batteries are connected with a conducting glue to produce a total voltage of 3.18 V and are fitted with brass wire contacts (0.3 mm ∅). Both ends of the battery compartment of the capsule are sealed. Two electrodes, arranged in parallel, at which the electrolytic breakdown of water occurs, are contained in the next section of the capsule at a distance of 2 mm from the battery compartment. The battery leads are passed out of the battery compartment through boreholes 0.8 mm in diameter. The negative pole is connected directly to a steel wire electrode (0.7 mm ∅). The connection to the second electrode is made via a magnetic switch (reed relay, 11 mm long, 1.6 mm ∅, (Fa. Merten-Electronic, Münster, Germany). All parts of the circuit are isolated with a thin layer of a rapid hardening glue (Pattex Stabilit, Fa. Henkel, Düsseldorf, Germany). The magnetic switch is activated by an electromagnet (220 V d.c., 0.58 A, Schultz, Memmingen, Germany) at a maximal distance of 12 cm. The electromagnet is operated by an IBM-compatible AT computer (High Screen, Taiwan) and a Centronics relay interface (UCR-80, Auerswald, Cremlingen, Germany).

60 μl of electrolyte solution (polysorbate 40 0.06 g, NaCl 0.05 g, 0.1 N HCl to 1.00 g) are placed in the capsule. A 4 mm thick agar gel disc (agar-agar 1.0 g, purified water to 25.0 g), separates the electrolyte region of the capsule from the region containing the drug. 120 μl of a metoprolol solution (2.1 g metoprolol tartrate, purified water 0.77 g) are pipetted into the drug reservoir. The capsule is sealed with a stopper which has a borehole of 1 mm and a valve, through which drug is only released on overpressure.

The construction of the model capsule with an external power supply is similar to that of the capsule with an internal supply, but because it contains no battery compartment, its length is 20 mm. The steel electrodes are connected to an external power source consisting of a power-pack (Voltkraft NG 15, Conrad, Herisau, Germany) which is computer-controlled via a Centronics relay interface.

Release experiments

The investigations of the release of metoprolol tartrate from capsules were carried out in 1000 ml 0.01 N HCl at 37°C in a USP XXII Paddle Apparatus at a speed of 35 rpm. The capsule was fixed in a horizontal position about 8 cm below the surface of the liquid whose temperature was controlled by a water bath. The electromagnet used to switch on the circuit of the capsule at the designated times was situated outside the water bath at a distance of about 10 cm. The amount of drug released was determined spectrophotometrically (Spectrophotometer Model 100–40, Hitachi, Tokyo, Japan) at 274 nm, using a flow-through cuvette (1 cm). The samples were collected by a peristaltic pump (STA-Schlauchpumpe, Desaga, Heidelberg, Germany) and filtered. The mean and standard deviation of five experiments were calculated. The experiments with an external

power supply were carried out in a similar way. A voltage of 1.5 V was used.

Results

The intention of the present experiments was to build prototypes of capsule-like model dosage forms allowing a variable control of the release of drugs. It was also planned to include the possibility of varying release by remote control. In a capsule of the intended maximal size of 25 mm, there is only a very limited space available for a drug reservoir, a variable pump mechanism, an energy source and a remote control system. Therefore, the simplest possible construction principles were chosen in this experiment. Fig. 1 illustrates the layout of the capsule in diagrammatic form and a photograph of the capsule is shown in Fig. 2. Two miniature batteries were used in these investigations and release is controlled by an electrical circuit and a microswitch. The drug is released by the pressure of the gases which are generated on the electrolytic breakdown of an aqueous solution of an electrolyte. A small disc of agar gel which separates the gas space from the drug reservoir acts as a piston. Other capsules with external power supply (Fig. 3) were included in the investigations for systematic study.

Metoprolol tartrate was added to the drug reservoir of the capsule as a highly concentrated solution. Diffusion of the drug substance from the reservoir, during the interval in which no release was to occur, was prevented by closing the release orifice with a simple valve. A schematic drawing of the valve is given in Fig. 4. Release is controlled via a computer interface, through the switching on and off of an electromagnet at certain time intervals. The microswitch in the circuit is engaged by the magnetic field. At the same time, gas begins to form through the electrolysis of the aqueous system and the agar piston pushes the drug solution out of the drug reservoir. In the case of the capsules with external power supply, the current is passed direct from an external power supply to the electrodes through the computer interface.

The release of metoprolol tartrate from the newly developed capsules was investigated using a wide variety of operating and pause times. The

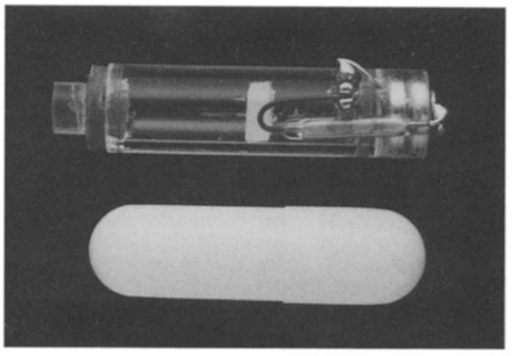

Fig. 2. Photograph of the capsule with internal power supply.

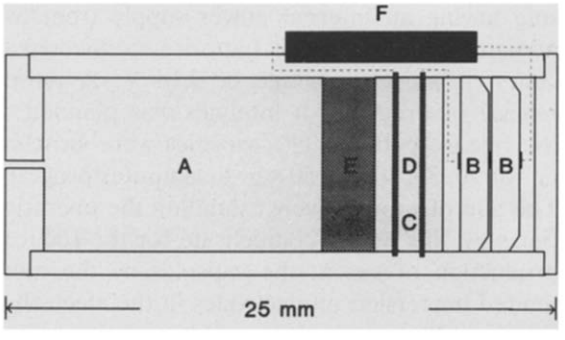

Fig. 1. Schematic diagram of the remote-controlled capsule. (A) Solution of drug, (B) miniature batteries, (C) electrodes, (D) electrolyte solution, (E) piston (agar disc), (F) magnetic remote-controlled switch.

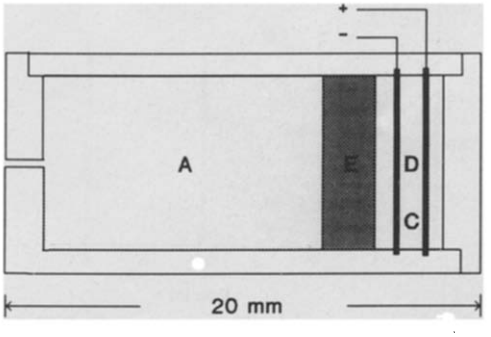

Fig. 3. Capsule with external power supply. (A) Solution of drug, (E) piston, (C) electrolyte solution, (D) electrodes.

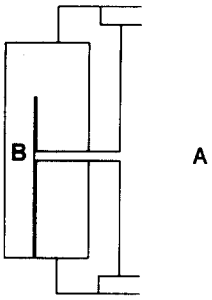

Fig. 4. Capsule valve made from soft plastic. (A) Capsule, (B) valve.

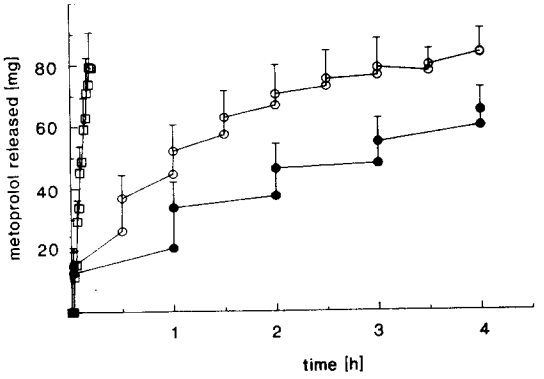

Fig. 5. Release of metoprolol tartrate from capsules with external power supply ($n = 5$, $\bar{x}$). (□) Operating time 30 s, pause time 120 s; (○) Operating time 30 s, pause time 30 min; (●) Operating time 30 s, pause time 60 min.

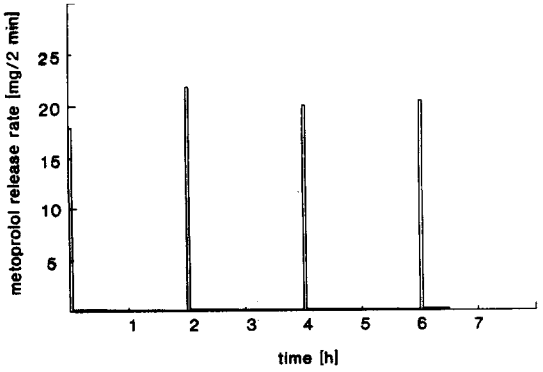

Fig. 6. Pulsed release of metoprolol tartrate from remote-controlled capsules ($n = 5$, $\bar{x}$). Operating time: 20, 30, 40, 50 s at intervals of 2 h.

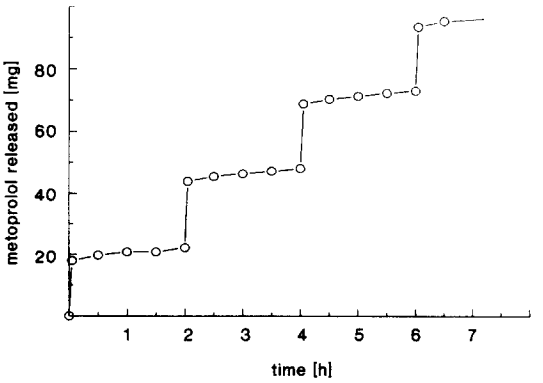

Fig. 7. Pulsed release (cumulative plot) of metoprolol tartrate from remote-controlled capsules ($n = 5$, $\bar{x}$). Operating time: 20, 30, 40, 50 s at intervals of 2 h.

results of the release experiments with capsules having an external power supply are illustrated in Fig. 5. This shows that the 80 mg metoprolol tartrate present in the drug reservoir can be released within a few minutes or over a extended period of several hours. If the power supply is switched on for 30 s, with a pause interval of 120 s, the release is complete within about 20 min. If the capsule mechanism is operated for 30 s at 30-min intervals, then release of 80 mg drug takes 4 h. By switching on for 30 s at intervals of 60 min, about 65 mg metoprolol tartrate is released over a period of 4 h.

Figs 6 and 7 show the release of metoprolol tartrate obtained with a remote-controlled capsule having an internal power supply from two miniature batteries. The batteries, connected in series, produce a voltage of 3.18 V. A pulsed release of drug at 2-h intervals was planned as the release pattern. The capsules were switched on for 20, 30, 40 and 50 s by a computer program. The aim of progressively extending the operating times by 10 s was to compensate for the reduced production of gas in the capsules by the more limited immersion of electrodes in the electrolyte solution. The results of the release experiments show that a pulsed release of about 20 mg metoprolol tartrate can be achieved at intervals of 2 h with the described operating program.

Discussion

The results of the experiments with the newly developed capsules demonstrate that it is possible to obtain a variable control of the release of active substance from small, capsule-like dosage forms. As shown by this present example, even higher dosages of drugs can be used than in our earlier experiments on the electrophoretic control of drug release from capsules.

The capsules used here contain a simple remote control device which can be operated over a distance of roughly 12 cm through the release apparatus with water bath and release medium. A commercial reed relay was used in these experiments. With stronger magnetic fields or electromagnetic systems, even greater distances could be crossed. It is conceivable that switches and switching circuits specially designed for drugs could be used for future dosage forms. Biodegradable systems might also be incorporated.

The capsules contain a simple pump mechanism which produces mechanical energy from electrical energy. The mechanism can be optimized in future by further development of the electrodes and the electrolytes. More improvements might be achieved through using other materials for separating the gas space from the drug solution or suspension. For example, an oleogel could be used as the piston. Fluted bag systems might also be employed to hold the drug.

With systems in which the release is based on measured values such as plasma levels, the accuracy of dosage is only of secondary importance. The use of electrical energy as the primary energy in drug dosage forms opens up further possibilities for using sensors and control elements.

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