Institute for Pharmaceutical Technology[1], University of Münster, Germany, Department of Pharmaceutical Sciences[2], Howard University, Washington, DC, USA, and Faculty of Pharmacy[3], Medical University Sofia, Bulgaria

Computer-controlled release of oxprenolol from capsules using small gas producing cells and electronic circuits

R. Gröning[1], S. Weyel[1], E. Akala[2], E. Minkow[3] and N. Lambow[3]

Dedicated to Prof. Dr. G. Zessin, Halle (Saale), on the occasion of his 65th birthday

In the present study new sustained release capsules were developed. In these capsules the drug release from a reservoir is controlled by a small dimensioned gas producing cell. The release mechanism is controlled by a computer program, an interface, an electro magnet and a magnetic switch. The pressure of the hydrogen gas controls the movement of a piston which empties the drug reservoir. Investigations with a solution of oxprenolol hydrochloride show that a pulsed release of about 140 mg of the drug was obtained within 60, 240 or 480 min.

1. Introduction

Normally the drug release from peroral sustained release dosage forms is controlled by passive processes like diffusion, erosion or degradation. An energy controlled release can be obtained with osmotic systems [1]. In the future drug delivery devices will become more and more important, which show a completely controllable drug delivery. The drug release may be adjusted to the special demand of the individual patient. To get a variable drug delivery the construction of new devices is necessary. Electrophoretically or electrolytically controlled systems were previously described by our group [2, 3].

In the present study, commercially available gas producing cells [4, 5] were used in the construction of small dimensioned model dosage forms. Gas producing cells were already used for technical applications to transport liquids and pastes, for example, to lubricate ball bearings [6]. The use of the gas producing cells for drug release from small dimensioned computer controlled model dosage forms was not previously described.

Gas producing cells look like small batteries. They are galvanic elements, in which a cell reaction (redox reaction) produces hydrogen gas. Fig. 1 shows a schematic diagram of the gas producing cell with a diameter of 7.8 mm. The beaker (1) and the cap (2) together with the gasket (5) make up the body of the gas producing cell. A zinc electrode (3) is used as an anode, which consists of either a zinc powder or a zinc gel with a cellulose derivative as a viscosity heightening additive. The gas is released through a small hole at the bottom of the beaker.

If the two poles of the gas producing cell are connected with a conducting path, then the cell begins to produce gas which is released via the opening located at the bottom of the beaker. The gas is produced from the cell reaction which is described as follows (Scheme).

Scheme

$$\begin{array}{lll} \text{Anode} & Zn^{\circ} + 2\,OH^{-} & \rightarrow Zn(OH)_2 + 2e^{-} \\ \text{Cathode} & 2\,H_2O + 2e^{-} & \rightarrow 2\,OH^{-} + H_2 \\ & \multicolumn{2}{l}{\text{---------- + ----------}} \\ & Zn^{\circ} + H_2O & \rightarrow Zn(OH)_2 + H_2 \end{array}$$

The anode reaction is the oxidation of zinc to zinc hydroxide. In the alkaline electrolyte, the consequent reaction is the decomposition of zinc hydroxide to zinc oxide and water. As cathode reaction, the reduction of water to hydrogen and hydroxide ions occurs. Due to the redox reaction where metallic zinc becomes a $zinc^{2+}$-ion solution, the cell produces gas until the entire anode is dissolved.

2. Investigations and results

In the present study a model dosage form was constructed in which an active remote controlled release of a drug can be obtained by an electrical circuit with a magnetic switch and a gas producing cell. The gas which is produced is used to drive the piston system of the drug reservoir. It was the aim of the study to get variable release kinetics by varying the intervals of activation of the capsule. Capsules which show a variable release may be used to administer drugs in therapy programs in the future.

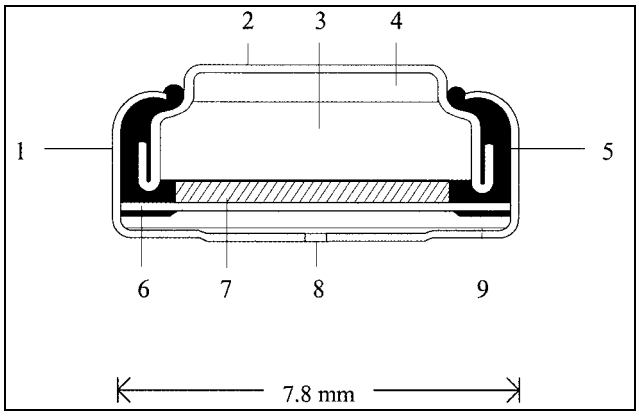

Fig. 1: Schematic diagram of a gas producing cell for installation into a magnetic remote controlled model dosage form. 1: Beaker, 2: Cap, 3: Zinc electrode, 4: Compressed unit, 5: Gasket, 6: Diaphragmatic layer, 7: Separator, 8: Release opening, 9: Working layer

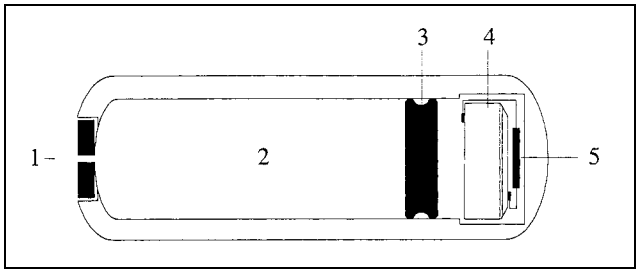

Fig. 2: Schematic diagram of a remote controlled magnetic dosage form with a gas producing cell; (length 25 mm, outer diameter 8 mm). 1: Release opening, 2: Drug reservoir, 3: Piston, 4: Gas producing cell, 5: Magnetic switch

Fig. 2 represents a schematic diagram of the remote controlled magnetic model dosage form with a gas producing cell.

Both poles of the gas producing cell (4) are connected with a thin copper wire. A magnetic switch (5) in the electric circuit interrupts the electric circuit when a magnetic field is absent. A piston (3) separates the electronic part of the capsule from the drug reservoir (2). The drug reservoir contains the drug solution. A ball valve prevents an uncontrolled release of the substance from the dosage form into the surrounding medium before the electrical circuit is activated.

By closing the magnetic switch, the hydrogen production starts. The hydrogen gas pushes the piston of the dosage form in the direction of the release opening. The drug solution is pressed through the valve into the surrounding release medium. The gas production persists until the circuit is interrupted due to switching off the magnetic field. As a result of the discontinued gas production, the movement of the piston and the release of the drug substance from the model dosage form stops.

In the present study oxprenolol hydrochloride was used as a model drug. The drug release was investigated using a computer program which enables to activate the capsules via a magnetic field for a specific time interval.

Fig. 3 presents the drug release from a computer controlled capsule when different pulse intervals (15 or 20 s) were applied. The time intervals between the pulses were two hours. Both curves show a pulsed drug release. The release rates are due to different pulse lengths. 140 mg oxprenolol hydrochloride are released within about 6 h when the capsule is activated three times for 20 s. When 15 s pulses were applied the same amount of the drug is released after 8 h.

Fig. 4 shows the release of oxprenolol hydrochloride from remote controlled capsules at varying time intervals. In all three experiments, a pulse time of 15 s was used. Depending upon the time intervals between the activation of the device, 140 mg oxprenolol are released within 1, 4 or 8 h.

In Fig. 5 the cumulative release of oxprenolol hydrochloride is plotted against time. The drug is released over a time period of 24 h. Between the first and second, as well as between the second and third pulse, there is a pause of 6 h. The last dose is released after 24 h. In all, after 24 h, nearly 140 mg of oxprenolol hydrochloride is released.

Fig. 6 shows the differential plot of the drug release. Within 3 min after every activation of the remote controlled capsule about 35 mg of the drug are released.

3. Discussion

In the present study, new small dimensioned computer controlled model dosage forms were developed, in which commercially gas producing cells were used to generate

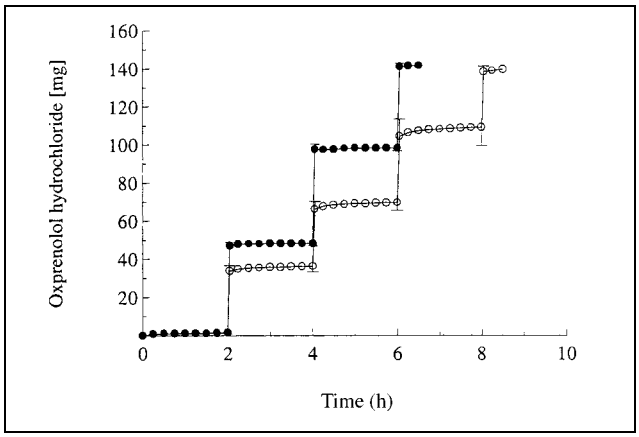

Fig. 3: Release of oxprenolol hydrochloride from remote controlled magnetic model dosage forms with gas producing cells; Interval 2 h; n = 5, arithmetic mean ± sd. –●– Pulse duration 20 s, –○– Pulse duration 15 s

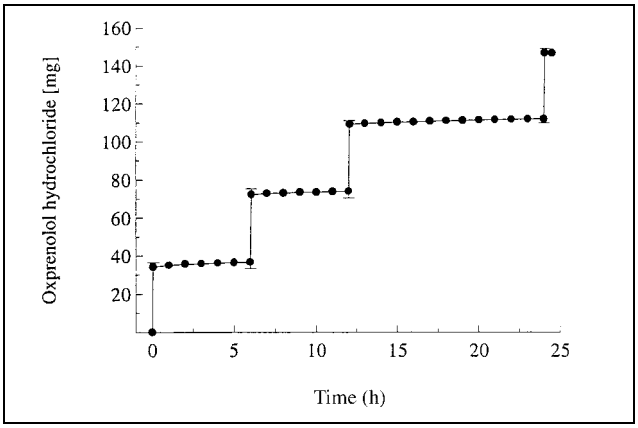

Fig. 5: Release of oxprenolol hydrochloride from remote controlled magnetic model dosage forms with gas producing cells; 15 s pulse at the beginning of the experiment and after 6, 12 and 24 h; n = 5, arithmetic mean ± sd

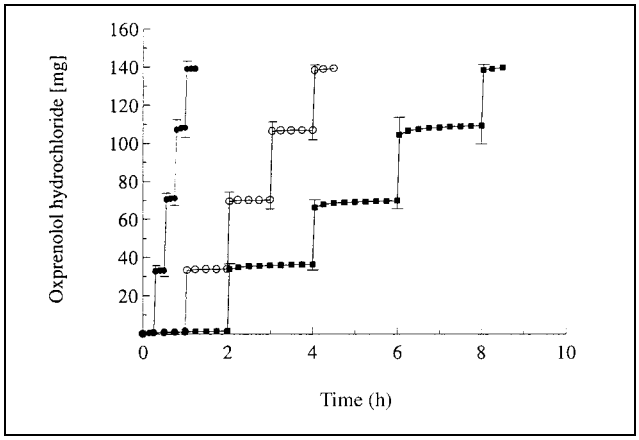

Fig. 4: Release of oxprenolol hydrochloride from remote controlled magnetic model dosage forms with a gas producing cell; 15 s pulse; n = 5, arithmetic mean ± sd. –●– Interval 15 min, –○– Interval 60 min, –■– Interval 120 min

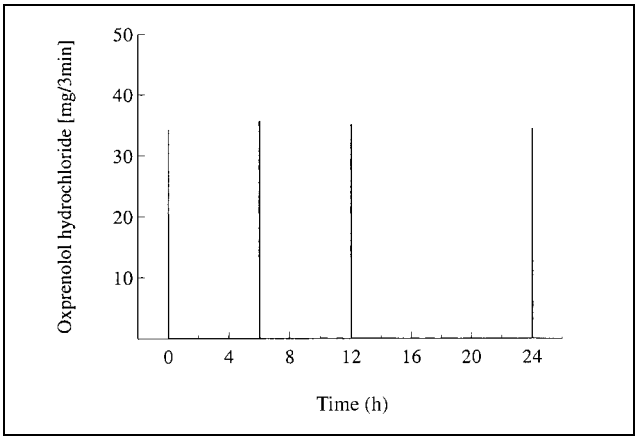

Fig. 6: Time dependent release rate (mg/3 min) of oxprenolol hydrochloride from remote controlled magnetic model dosage forms; pulse 15 s; activation of the capsule at the beginning, after 6, 12 and 24 h; n = 5, arithmetic mean ± sd

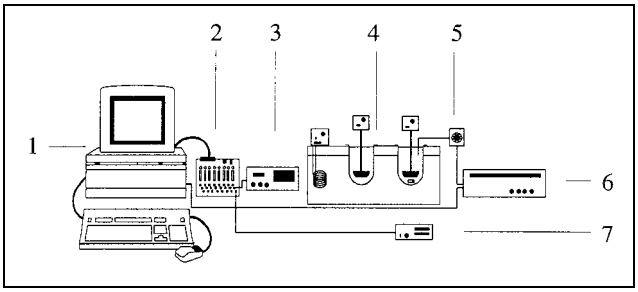

Fig. 7: Computer controlled drug release using magnetic remote controlled capsules. 1: Computer, 2: Interface, 3: Power supply, 4: Paddle apparatus, 5: Multichannel tubing pump, 6: Spectrophotometer, 7: Electromagnet

hydrogen gas to control the drug release. Using gas producing cells it is not necessary to integrate additional energy sources into the device. Questions concerning the stability of the cells should be investigated in the future.

Compared with other energy controlled drug delivery systems like oral osmotic systems, with the new devices it is possible to get variable release patterns which may be adjusted to the individual demands of a patient. Using a computer controlled system it is possible to get a real programmed release. The expression "programmed release" is sometimes used by other groups to describe traditional sustained release drug delivery systems.

Computer controlled devices similar to the new constructed system may be used as a peroral depot systems in the future. Investigations about the toxicity and environmental questions should be taken into consideration. Another important question is the control of the gastrointestinal transit of the device. New techniques to fix a delivery system in the gastrointestinal tract may be used.

The newly developed systems were constructed to get experience with the computer control of small sized devices. In the future biodegradable materials may be used to construct controlled release systems. Instead of the magnetic field for a remote control high frequency transmitters may be used [7].

4. Experimental

4.1. Model dosage form

The capsules were prepared from the front part of an insulin syringe (Omnifix®-F 1 ml, SOLO, Braun, Melsungen, Germany) with an internal diameter of 4.7 mm. The reservoir part of the capsule has a length of about 19 mm. The original piston of the syringe was shortened (5 mm) and used in the experiments.

A commercially available gas producing cell (Simatec, CH-Herzogenbuchsee) with a height of 3.6 mm and a diameter of 7.8 mm was attached to the back of the capsule. The poles of the gas producing cell were connected via a magnetic switch (6.4×1.8 mm, MITI-3, Hamlin, Bad Vilbel, Germany). The gas producing cell and the magnetic switch were covered with a thin film of two-component glue (Pattex Stabilit, Henkel, Düsseldorf, Germany).

Oxprenolol solution (210 µl, 1.2 g oxprenolol hydrochloride, 0.6 ml purified water) was pipetted into the reservoir. The capsule was sealed with a ball valve [8].

4.2. Release experiments

Release experiments with oxprenolol hydrochloride were carried out in the paddle apparatus Pharm. Eur. 1997 at 37 °C. The dissolution medium was 1000 ml 0.1 N HCl. The rotating speed of the paddle was 100 rpm. Fig. 7 shows a schematic diagram of the dissolution apparatus, the spectrophotometer, the electromagnet and the computer to control the drug release.

The electromagnet (100 W, Schüler-Magnetik, Dortmund, Germany), was placed outside the water bath. The amount of oxprenolol hydrochloride was measured spectrophotometrically (Hitachi Spectrophotometer Type U 1100, Hitachi, Tokyo, Japan) in the release medium at a wavelength of 272 nm with a 1 cm flow-through cuvette. A multichannel tubing pump (Type STA-Peristaltic pump, Desaga, Heidelberg, Germany) was used for continuous sampling. After the measurement the medium was leaded back to the dissolution vessel. The release studies were controlled with the help of a computer (IBM-compatible 80386/40, Escom Computer, Heppenheim, Germany), which switched on the electromagnet via an interface (Centronics relay interface UCR 80, Conrad-Electronic, Hirschau, Germany) at a certain interval and which registered the measured values. The power supply for the relay interface was 12 V AC.

The measured values were simultaneously recorded by an analog recorder (Type Servogor RE 511, Metrawatt, Nürnberg, Germany). Mean and standard deviation of 5 experiments were calculated.

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Received December 11, 1998
Accepted January 15, 1999

Prof. Dr. R. Gröning
Institute for Pharmaceutical Technology
Corrensstr. 1
D-48149 Münster
groenin@uni-muenster.de