European Journal of Pharmaceutics and Biopharmaceutics 72 (2009) 282–284

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Note

High frequency controlled capsules with integrated gas producing cells

Ruediger Groening *, Hubert Bensmann

Institute of Pharmaceutical Technology and Biopharmaceutics, Westfälische Wilhelms-Universität Münster, Münster, Germany

ARTICLE INFO

Article history:
Received 23 July 2008
Accepted in revised form 13 January 2009
Available online 20 January 2009

Keywords:
High frequency energy transmission system
Controlled drug release
Remote control
Gas generating reactor
Oxprenolol

ABSTRACT

In the present investigations, a new high frequency remote-controlled capsule has been developed in which the mechanical energy to empty a drug reservoir is generated by a miniature gas producing cell. If the poles of the gas producing cell are connected by an electric circuit, the gas production starts. The rate of gas production can be regulated by a resistor in the electric circuit and by the duration of activation of the system. To get a remote control, we developed a small receiver which is located inside the capsule. The receiver consists of an oscillating circuit, which is in resonance with an external 24 MHz high frequency transmitter. A MOSFET transistor acts as a switch in the electric circuit to start the gas production. Release experiments with oxprenolol show that different release patterns can be obtained.

1. Introduction

In the last years, different attempts have been made to modify the drug-release rate or to get a variable release from drug delivery systems [1–9]. It is the aim of our research in this field to orientate the drug release from dosage forms towards the demand of the individual patient. The new variable-controlled systems consist out of a drug reservoir, an energy source and a pump mechanism, which can be activated on demand. In papers already published or submitted for publication, we reported about systems which contain small gas producing cells [10,11]. The release mechanism in these systems was activated by magnetic fields or by sensor elements. In the case of the existing systems, which can be used to get information about the absorption of drugs, high frequency fields are used to start the drug release in a special area of the GI-tract [12–14]. Magnetically controlled systems with internal magnetic micro switches can only be activated over a short distance of about 100–150 mm. In vitro experiments show that by using this principle it will be possible to activate orally administered capsules in the colon by a magnetic patch, which is located on the surface of the body in the area of the colon [15].

In the presented investigations, we intended to develop capsules, which can be activated by a high frequency signal from outside the body.

2. Materials and methods

2.1. Materials

Oxprenolol hydrochloride was purchased from Sigma (Deisenhofen, Germany). Hydrochloric acid was from Merck (Darmstadt, Germany).

2.2. Development of dosage forms

A capsule-shaped model drug was constructed, which contained a gas producing cell and a receiver system (Fig. 1). The model dosage form was 28 mm in length and maximal 8.5 mm in diameter. The body of the capsule was manufactured using a polypropylene cylinder (length: 14.5 mm, diameter: 6.7 mm). A piston with a height of 2.0 mm and a length of 4.8 mm was placed in the cylinder. The piston separated the gas producing cell and the drug reservoir. The drug reservoir contained 0.17 ml of an aqueous solution of oxprenolol hydrochloride (c = 0.7 g/ml). The feed opening of the drug reservoir was sealed using a rubber form. The drug solution could be released through a bore hole in the sealing with a diameter of 0.6 mm. The gas producing cell (height: 3.5 mm, diameter: 7.8 mm) (size 3, Simatec, Herzogenbuchsee, Switzerland) was glued onto the cylinder using Loctide 406 (Loctide, München, Germany).

The electric circuit (Figs. 1–5), which was placed next to the gas producing cell, consisted of a small coil (3.3 μH) (Conrad Electronic, Hirschau, Germany), a SMD trim condenser (KTS-SMD, 13–50 pF) (Conrad Electronics, Hirschau, Germany), two SMD Skottky diodes (BAR 43 S) (Farnell-Electronic, Deisenhofen, Germany)

* Corresponding author. Institute of Pharmaceutical Technology and Biopharmaceutics, Westfälische Wilhelms-Universität Münster, Corrensstr. 1, D-48149 Münster, Germany. Tel.: +49 251 8339860; fax: +49 251 8339308.
E-mail address: groenin@uni-muenster.de (R. Groening).

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doi:10.1016/j.ejpb.2009.01.003

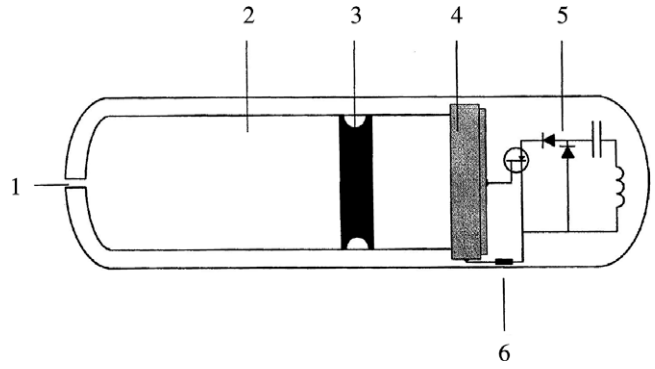

Fig. 1. Schematic diagram of a remote-controlled capsule with a gas producing cell and a high frequency receiver to control drug release, (1) feed opening, (2) drug reservoir, (3) piston, (4) gas producing cell, (5) high frequency receiver with integrated transistor, (6) resistor.

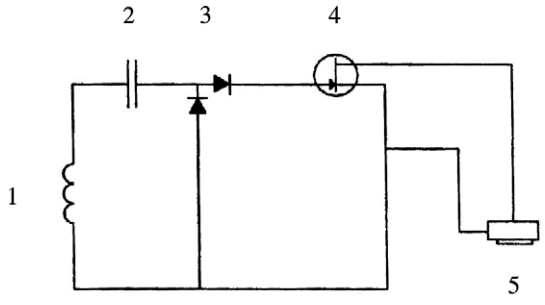

Fig. 2. Circuit diagram of the capsule electronics.

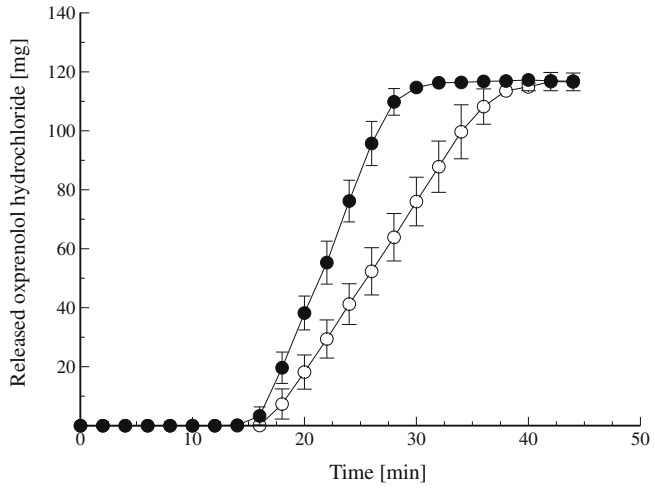

Fig. 3. Release of oxprenolol hydrochloride from remote-controlled capsules with a gas producing cell, a high frequency receiver and an integrated resistor; activation of the system after 10 min; $n = 5$, arith. means ± s, -●- 100 Ω resistor, -○- 200 Ω resistor.

and a MOSFET transistor (ZVN 4306 A) (Farnell-Electronic, Deisenhofen, Germany). It was possible to attune the electric oscillating circuit to the high frequency field by adjusting the trim condenser. The induced voltage was used to switch the transistor. To isolate the electric circuit, it was enclosed using glue (Pattex Stabilit, Henkel, Düsseldorf, Germany).

If a resistor was needed, a SMD resistor (0805, 0.1 W, Conrad Electronic) was integrated into the conducting circuit between the poles of the gas producing cell.

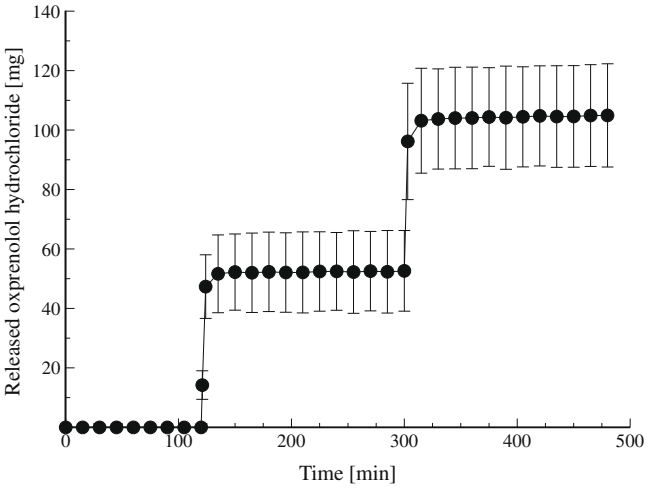

Fig. 4. Release of oxprenolol hydrochloride from remote-controlled capsules with a gas producing cell; activation after 2 and 6 h, pulse: 60 s, $n = 5$, arith. means ± s.

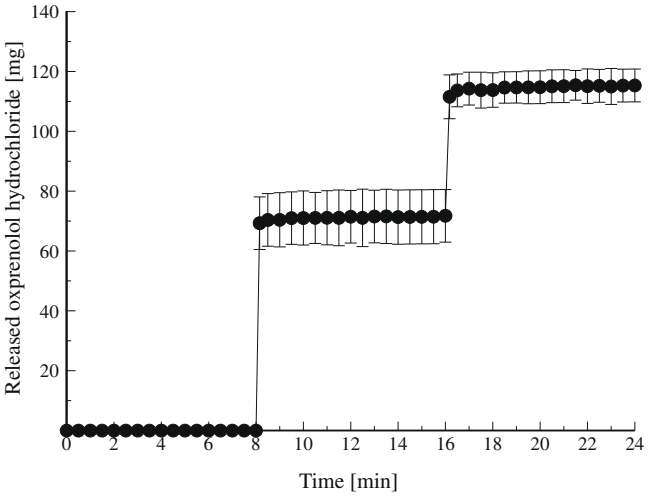

Fig. 5. Release of oxprenolol hydrochloride from remote-controlled capsules with a gas producing cell; activation after 8 and 16 h, pulse: 60 s, $n = 5$, arith. means ± s.

2.3. Drug release

A modified paddle apparatus (Ph. Eur., 50 rev./min) was used for dissolution studies. The paddle was manufactured and consisted of Plexiglas to avoid interference. Hydrochloric acid of 0.01 N (1000 ml/batch) was used as dissolution medium. The dosage forms were fixed in the batches 70 mm below the medium surface using Plexiglas tubes. After an equilibration time of 15 min (medium temperature 37 °C), the experiment was started. The distance between the antenna and the high frequency receiver was 150 mm. The amount of drug released was determined spectrometrically at a wavelength of 273 nm in a flow-through cell of a Hitachi U1100 (Hitachi, Tokyo, Japan). The measured values were continuously recorded and saved electronically.

3. Results and discussion

Small gas producing cells are available with diameters of 6 or 8 mm. They have the appearance of small watch batteries. If the plus and the minus poles of the gas producing cells are connected by a conductor, the hydrogen gas production starts. In the present investigations, a capsule was constructed which contains a gas

producing cell. The drug reservoir, which contains a drug solution or suspension, can be emptied by means of a piston, which is moved forward by the pressure of the hydrogen gas. The release mechanism of the capsule is switched on as long as a high frequency field induces a current inside an oscillating circuit. The high frequency signal was generated by a commercially available 24 MHz transmitter with an energy level of 4 W. The plus and the minus poles of the gas producing cell are directly connected if there is a gate source voltage at the MOSFET transistor. A schematic diagram of the capsule is shown in Fig. 1. The capsule has a length of about 25 mm and a diameter of 8 mm. A detailed circuit diagram is shown in Fig. 2.

To get a resonance between the high frequency transmitter and the receiver inside the capsule, it is necessary to adjust the oscillatory circuit to the frequency of the 24 MHz transmitter. The data of the capacitor and the coil, which are important to get a resonance, are given in Fig. 2. Two diodes act as rectifiers in the electric circuit. The rate of hydrogen, which is generated by the gas producing cell, can be regulated by means of a resistor in the conducting circuit. Drug-release experiments were performed using a 100- or 200-Ω resistor, which were integrated into the conducting circuit between the poles of the gas producing cells. In Fig. 3, the release curves of oxprenolol are plotted. The release was started by the high frequency signal after 10 min. If the hydrogen production is regulated by means of a 200-Ω resistor, it takes about 25 Ω min until the drug reservoir is emptied. If a 100-Ω resistor is a part of the electric circuit, the drug is released within 15 min.

In further experiments, capsules without resistors were used. To get a pulsed drug delivery, the release mechanism of the capsules was activated twice after 2 and 6 h or in another experiment after 8 and 16 h. The release curves are plotted in Figs. 3 and 4. The results show that it is possible to activate the remote-controlled capsule on demand after intervals of some hours and to get a controlled and reproducible release of the drug. Different amounts of the drug are released after 8 and 16 h. This difference may be caused by a loss of gas pressure in the gas producing cell.

The high frequency controlled capsules were developed to get preliminary information about high frequency remote-controlled drug release. The capsules, which we used in the investigations, are not biodegradable. In future, it may be advantageous to construct delivery systems, which are biodegradable in the sewage after defecation. The electronic circuits should be built up using printed connectors and degradable electronic elements.

Another important issue is the high frequency signal. The system, which we developed in our investigations, is a nonspecific energy transmission system. In future, it will be important to generate a specific high frequency signal, which only activates one individual capsule.

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