International Journal of Pharmaceutics 364 (2008) 9–13

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Control of drug release from capsules using high frequency energy transmission systems

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ARTICLE INFO

Article history:
Received 16 April 2008
Received in revised form 1 July 2008
Accepted 2 July 2008
Available online 16 July 2008

Keywords:
High frequency energy transmission system
Delayed drug release
Pulsed release
Gas generating reactor
Tramadol

ABSTRACT

In the present investigations new drug delivery systems have been developed, which are controlled by a computer and a high frequency energy transmission system. The capsules consist of a drug reservoir, a high frequency receiver, a gas generating section and a piston to pump a drug solution or drug suspension out of the reservoir. Mechanical energy is generated inside the capsule through electrolysis, if a 27 MHz high frequency field is in resonance with the receiver inside the capsule. Two different miniaturised oscillatory circuits were constructed, which act as the receivers in the capsules. Tramadol was used in release experiments as a model drug. Delayed and pulsed release profiles were obtained. A computer-controlled system was constructed, in which the programmed release profiles are compared with the actual release of the drug.

1. Introduction

Energy transmission systems based on high frequency electric fields and oscillatory circuits are used in medical devices like artificial hearts, cochlea implants or in remote controlled sensor systems to influence or measure body functions (Gstoettner et al., 2000; Zierhofer and Hochmair, 1992; Snyder et al., 1993; Ahn et al., 1993; Helmicki et al., 1996; Pavie et al., 2003; Troyk and Schwan, 1992; Weiss et al., 1989; Fryer et al., 1978). Electric field exposure may result in bioelectric interaction (Reilly, 2002). But at time there has been no evidence of adverse reactions in patients caused by the electromagnetic fields. In the present investigation high frequency fields were used to control drug release. This is a new attempt to get an active and variable drug release from drug delivery systems. Existing systems like the "high frequency capsule" (Laufen and Wildfeuer, 1987; Schuster and Hugemann, 1987) or the InteliSite® capsule (Clear et al., 2001; Pithavala et al., 1998) use high frequency fields to start the release of a drug in a special area of the GI-tract to get information about the absorption of drugs from the GI-tract. In these systems the drug reservoir is emptied at once, if a high frequency signal has activated the capsules. It is not possible to get a controlled and variable drug release from these systems. Based on the previous work of our group it is the aim of the present investigations to develop drug delivery systems which are controlled by high frequency energy transmission systems to get individual drug release profiles.

2. Materials and methods

2.1. Materials

Tramadol hydrochloride was purchased from Synopharm (Barsbüttel, Germany). Sulphuric acid and hydrochloric acid were from Merck (Darmstadt, Germany).

2.2. Development of dosage forms

The new capsule-like dosage form was build up from a polypropylene cylinder, a PVC mould, a plug and the electrical circuits. The cylinder had dimensions of 16.0 or 20.0 mm × 6.7 mm. The inner diameter was 4.2 mm. The mould (5.5 mm × 8 mm) was screwed onto the cylinder. A rubber ring was used to seal the system. The electrodes, which consisted of platinum conductors (15 mm × 0.25 mm), were placed parallely to the longitudinal axis of the system. They were fixed in perforations in the mould using glue (Pattex Stabilit, Henkel, Düsseldorf, Germany). The electrical circuits were connected with the conductors using conducting glue (Elecolit 325 A + B, Panacol-Elosol, Frankfurt, Germany). The electrical circuit was manufactured using a SMD trim condenser (KTS-SMD, 13–50 pF) (Conrad-Electronics, Hirschau, Germany), a small coil (3.3 μH) and two SMD Skottky diodes (Farnell-Electronic, Deisenhofen, Germany), which had been connected in series.

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doi:10.1016/j.ijpharm.2008.07.007

Fig. 1. High frequency controlled drug delivery systems with an energy transmission system, (A) oscillatory circuit (high frequency receiver), (B) drug reservoir, (C) piston and (D) electrolysis chamber with two platinum electrodes.

The high frequency receiver was glued onto the mould (Pattex Stabilit). The electrolytic cell (4.5 mm × 4.5 mm) was filled with 0.06 ml 3N sulphuric acid. A rubber piston (vulcanisable rubber, PH 7016/50/LC) (2.0 mm × 4.8 mm) separated the sulphuric acid and the drug reservoir. The reservoir contained 150 μl or 200 μl drug solution. A rubber form was used to seal the reservoir. A bore (diameter 0.6 mm) in the cap made release of the drug solution possible.

Further, a dosage form with an electric circuit with three coils was constructed. The Plexiglas body of the dosage form was cylindrical with a length of 10.5 mm and a radius of 8.5 mm. The cylinder was drilled to form the electrolytic cell (length: 2 mm, diameter: 4.0 mm) and a cell for the electrical circuits (8.0 mm × 6.5 mm). The electrolytic cell was filled with cotton and with 25 μl 2N sulphuric acid. The electrolytic cell and the circuit cell were separated by a plastic disc. Two platinum conductors were led through small wells in this disc. The platinum electrodes were connected to the high frequency receiver. The electrical circuit was manufactured using three SMD condensers (type 0805, 1–3.9 pF) (Conrad-Electronics, Hirschau, Germany) and six SMD Skottky diodes (BAR 43 S). Three framework coils with an inner diameter of 5.0, 5.25 and 5.5 mm were arranged as a cubic. The SMD condensers and the SMD Skottky diodes were placed inside this cubic. The coils in combination with one of the condensers and two SMD Skottky diodes formed the electrical oscillating circuits. The circuit cell was sealed by a Plexiglas cap using glue (Loctite 406, Loctite, München, Germany). The drug reservoir was connected by an external thread (2.0 mm × 7.0 mm). The connection was sealed by a rubber ring. The reservoir was build up from a polypropylene cylinder (12.5 mm × 8.6 mm). A rubber piston (2.0 mm × 6.5 mm) separated the sulphuric acid and the drug reservoir. The reservoir was filled with 0.225 ml tramadol solution (2.2 g tramadol hydrochloride/ml). It was sealed by an electrovalve.

2.3. Drug release

Dissolution studies were performed using a modified paddle apparatus (Ph. Eur., 50 revolutions/min). The paddle was manufactured from Plexiglas to avoid interference. In case of the dosage form with one coil, the dissolution medium was demineralised water, in case of the system with three coils 0.1 N hydrochloric acid (1000 ml/batch). The dissolution medium had a temperature of 37 °C. The dosage forms were placed in the batches 15 min before start of the measurements. The single-coil dosage forms were fixed in a vertical position 70 mm below the liquid surface using Plexiglas tubes. The transmitting antenna was placed in a distance of 60 mm. The multi-coil dosage forms were fixed with glass tubes at the bottom of the batches in a distance of 5–70 mm to the transmitting antenna. The tramadol hydrochloride release was measured UV spectrometrically at 272 nm in a flow-through cell of a Hitachi U1100 (Hitachi, Tokyo, Japan). The measured values were continuously recorded and saved electronically.

The drug release was controlled via a computer program by activating or deactivating the dosage forms. To get different release profiles, different programmes were developed. The programming language was Basic. In the experiments with the three-coiled dosage form, the programming controlled the drug release and compared the measured drug release with a pre-programmed release pattern. The programs included collection and processing of external data input, calculation of the expected drug release, control of the dosage forms and collection of experimental data. The dosage forms were activated by a 27 MHz-high frequency genera-

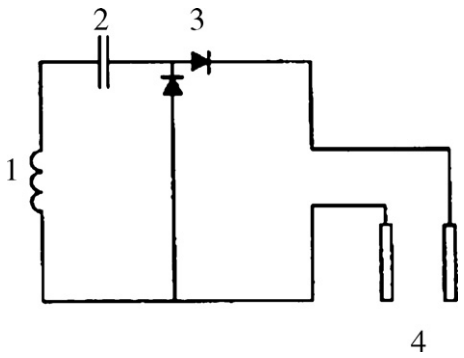

Fig. 2. Oscillatory circuit with one coil, (1) coil (3.3 μH), (2) capacitor (13–50 pF), (3) diodes (BAR 43 S) and (4) platinum electrodes.

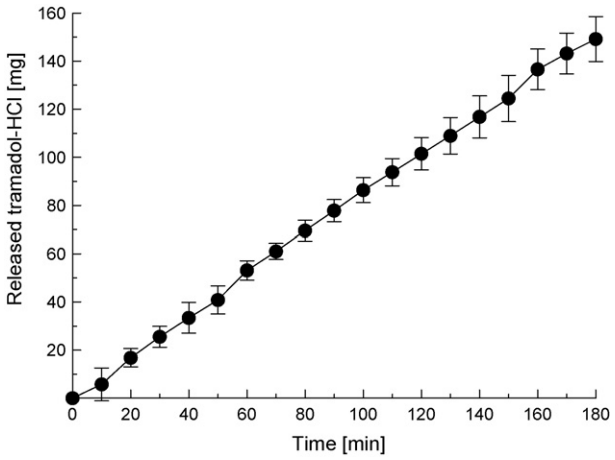

Fig. 3. Release of tramadol hydrochloride from capsules, if the high frequency field is activated constantly.

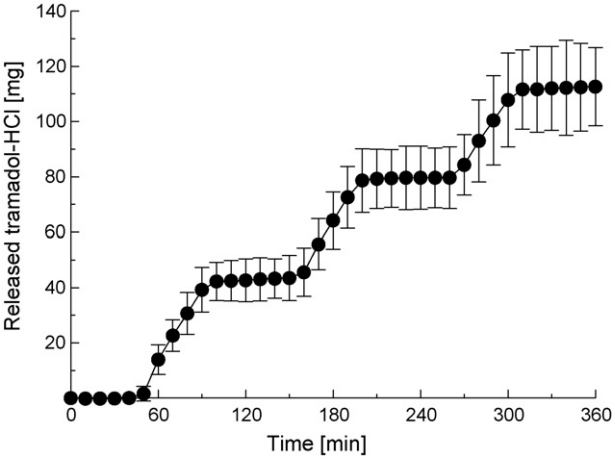

Fig. 4. Pulsed release of tramadol hydrochloride from capsules, if the high frequency field is activated discontinuously.

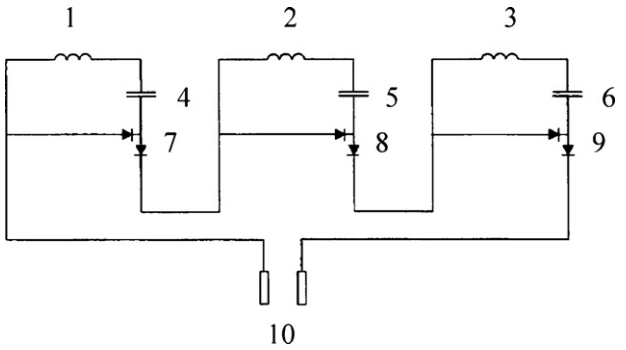

Fig. 5. Electric circuit with three coils. (1)–(3) coils (3.3 μH), (4)–(6) SMD condensers, (7)–(9) diodes (BAR 43 S), (10) platinum electrodes.

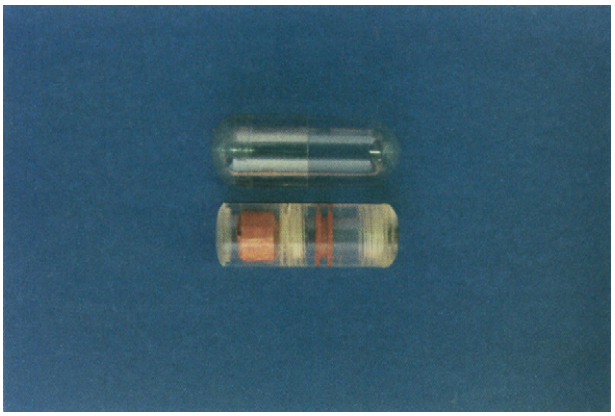

Fig. 6. Photograph of a capsule with a high frequency energy transmission system.

tor, for which a special ring antenna had been constructed. The ring antenna (diameter 300 mm) consisted of a copper cable (single-wire, Kortenbrede, Münster, Germany) with a core diameter of 2.3 mm. A trim condenser and an open ring with a diameter of 85 mm were soldered with the big copper ring. The antenna was connected with the high frequency generator via a coax cable (RG 58, Conrad-Electronic, Hirschau, Germany). A CB transmitting set was used as high frequency generator.

3. Results

In the present investigations new capsule-like drug delivery systems were developed, which consist out of a drug reservoir, a high frequency receiver, a gas generating section and a piston to pump a drug solution or drug suspension out of the reservoir (Fig. 1). Mechanical energy is generated inside the capsule through the elec-

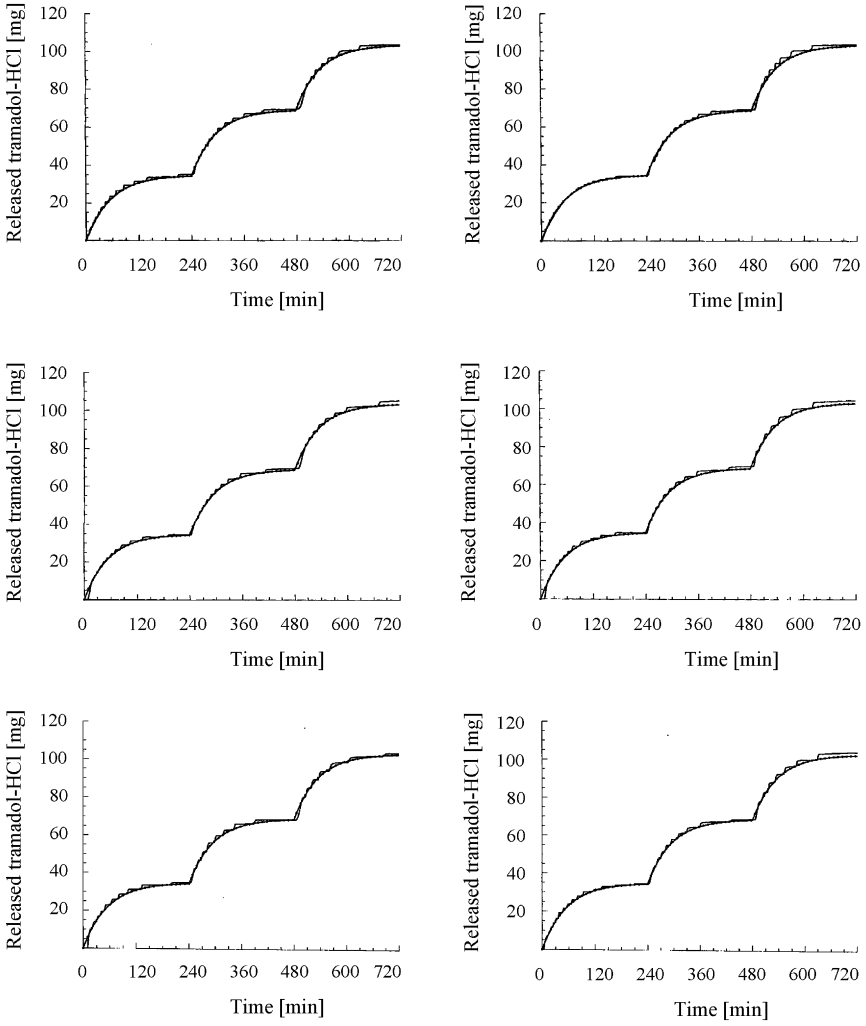

Fig. 7. Pre-programmed and obtained tramadol release from capsules.

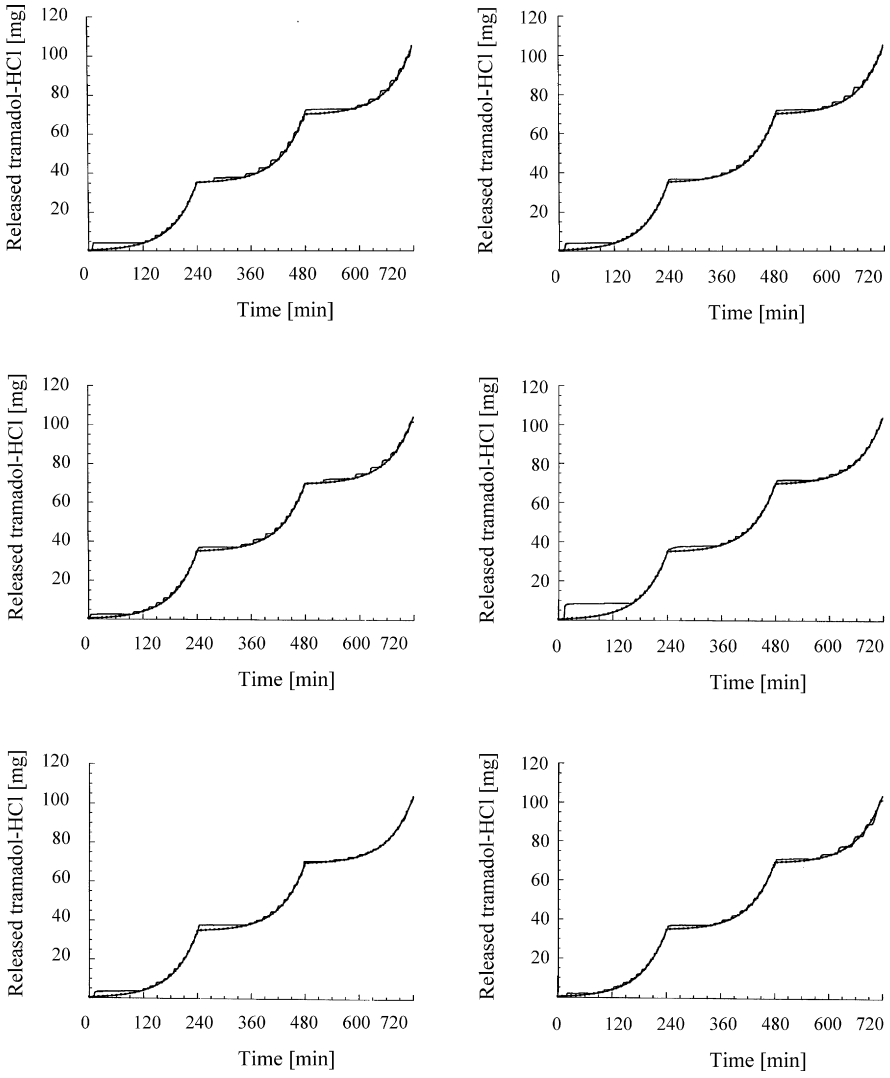

Fig. 8. Pre-programmed and obtained tramadol release from capsules (inverse profiles).

trolysis of acidified water. The pressure of the oxygen and hydrogen, formed at the platinum electrodes, moves the piston forward. The drug reservoir is emptied. A valve at the release opening ensures, that the drug solution is only released from the reservoir when the piston is moved forward.

The oscillatory circuit of the capsule is in resonance with the 27 MHz electromagnetic field and acts as the high frequency receiver. Two diodes in the circuit ensure that the electrodes in the electrolysis chamber are polarised as anode and cathode, whenever the electromagnetic field is switched on. Experiments confirmed that in the new capsular system the polarisation of the electrodes resulted in electrolysis of water. Fig. 2 shows the construction principle and the data of the oscillatory circuit with one coil. The oscillatory circuit acts as the receiver in the capsule. It is necessary to orientate the capsules, which contain only one oscillatory circuit, in a defined position in the high frequency field. Electrolysis will only take place, if enough energy is generated in the electric circuit. To achieve this, a perfect resonance between the transmitter and the receiver is necessary. To get a resonance with the high frequency field, the inductivity of the coil was calculated using the following equation:

$$L = \frac{0.02d^2n^2}{d + 2b}$$

If the inductivity of the coil is known the resonance capacity of the oscillatory circuit can be calculated directly:

$$C = \frac{25300}{f_0^2 L}$$

Release experiments were carried out with capsules, which were filled with a solution of tramadol hydrochloride. If the high frequency field transmits the electric energy constantly, the drug is released with a constant rate over a time period of 180 min (Fig. 3).

A pulsed release of tramadol hydrochloride is obtained, if the high frequency field is discontinuously activated for 45 min (Fig. 4). The high frequency field was switched on after 45 min. The release of tramadol hydrochloride started with a slight delay after 50 min. About 120 mg of the drug were released after 6 h.

To get reproducible results it is necessary to fix the described capsule in a defined position in the high frequency field. It was the aim of the present investigations to build a capsule, in which the energy transmission is independent of the position of the capsule in the electric field. Therefore, an electric circuit with three coils was constructed. The coils were orientated in three different directions, so that there is a resonance with the high frequency field, which is independent of the orientation of the capsule towards the transmitter. The electric circuit is shown in Fig. 5. A photograph of

the capsule is shown in Fig. 6. A hard gelatine capsule (size no. 00) is used as reference dosage form.

To get individual and reproducible drug release kinetics a computer controlled system was constructed, in which the drug release is automatically controlled and compared with the preprogrammed release pattern. The high frequency field is only activated, if the measured drug concentration is lower than the desired concentration. Two different release profiles were programmed to get a pulsed release. The profiles were chosen to get information about the possibilities and limits of a computer controlled drug delivery from the newly constructed capsules. During drug therapy in man the profiles should be orientated at the demand of the patients. In Figs. 7 and 8 the individual release profiles of tramadol hydrochloride are shown in comparison with the programmed profiles. The drug release is directly consistent with the calculated profiles. To get such identical profiles, it is necessary that the high frequency field be switched off a little bit earlier before the programmed concentration of the drug in the release medium is obtained. As a result the delayed drug release, which occurs after switching off the high frequency field, can be compensated. Using this technique, the drug concentration can be kept in the programmed range and surplus concentrations are avoided.

4. Discussion

By using a computer-controlled system the differences in energy transfer and drug release are compensated, which may occur due to differences in the distance between transmitter and receiver. If the transmitted energy is lower, the system will be activated for a longer time until the programmed amount of the drug is released.

Our in vitro studies were carried out in aqueous release media. It is known that the high frequency signal will pass as well through dissolution media as through body fluids and tissues. Other authors reported about the use of high frequency signals to start drug release, e.g. from the InteliSite® capsule (Clear et al., 2001; Pithavala et al., 1998).

In drug therapy in a man, it will be necessary to monitor plasma concentrations to get a feed back controlled system.

It is well known that there are other systems for drug targeting into the GI tract. In most cases the release is controlled by passive processes like pH dependant dissolution of polymer films. In our studies an actively controlled system is used. It is not only possible to control the start of the drug release, but it is also possible to control the release profile.

The developed capsules are complex systems, which are not intended for routine use in patients. Our current studies should give basic information about remote controlled and variable releasing drug delivery systems. In the future systems with commercially produced miniaturized circuits may offer a chance to reduce the costs.

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