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Development of sensor elements to control drug release from capsular drug delivery systems

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Abstract

The objective of this study was to develop a capsular drug delivery system, which releases the drug when a sensor element is activated by gastrointestinal fluids. The sensor element consists of a microswitch and a control membrane. After disintegration or dissolution of the control membrane the gastrointestinal fluid switches on an electric circuit. Via a gas producing cell the drug reservoir of the capsule is emptied within 6 min.

In vitro experiments with pH-sensitive polymethacrylic sensor membranes (Eudragit S 100) show that prednisolone dihydrogenphosphate is released within a few minutes when the capsule is transferred from gastric juice to artificial intestinal fluid of pH 6.8. Experiments with sensor elements prove that the membrane thickness influences the response time of the sensor. When 32 μm membranes are used, the electric circuit is switched on with a delay of about 70–80 min at pH 6.8. The developed systems are intended to be used as pump systems to deliver drugs into specific areas of the gastrointestinal (GI) tract.

Keywords: Sensor elements; Controlled drug release; Drug delivery systems; Capsule

1. Introduction

Polymer coatings are used to control drug release from tablets or capsules into specific sites of the intestinal tract (Khan et al., 1999; Ishibashi et al., 1998; Gupta et al., 2001; Bronsted et al., 1998; Sangalli et al., 2004). Polymers, which are pH-sensitive, or coatings, which undergo fermentation by bacterial enzymes, control the onset of release (Khan et al., 2000; Cheng et al., 1994; Hirsch et al., 1995; Lorenzo-Lamosa et al., 1998). A sufficient thickness of the coating is necessary to get mechanically stable systems, which can be ingested without damage (Bussemer et al., 2003b). During the transit to the desired region of the GI tract no drug release should take place. For several drugs a complete release after a defined lag time or in a specific site of the intestinal tract, e.g., in the colon, is advantageous. A potential problem of film coated systems is the not immediate drug release after the loss of the barrier function. To get an immediate drug release rupturable systems are described (Krogel and Bodmeier, 1999; Bussemer et al., 2003a; Sungthongjeen et al., 2004; Dashevsky et al., 2004). Another approach is the Pulsincap® system, which consists out of an insoluble capsule body and a swellable plug (Binns et al., 1996; Wilson et al., 1997; Stevens et al., 2002).

In the future drug delivery devices, which release the drug via an active release mechanism, will become more and more important (Gröning, 1997). The objective of the present study was to develop drug delivery systems, in which the onset of the drug release is controlled by sensor elements. The new systems are based on capsules consisting of insoluble capsule bodies with a drug reservoir and a small gas producing cell which can be activated by a sensor element.

2. Materials and methods

2.1. Development and testing of a membrane controlled sensor element

A sensor element was developed consisting of electrodes, a cellulose depot and a membrane, all fixed in a tube. The tube material was polystyrene (Polystyrol® 158 K glasklar Q 215, BASF, Germany). Two platinum electrodes were fixed in the

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upper area of the tube. The electrodes form a microswitch. They were arranged in a slight distance to each other and to a depot of compressed cellulose. A membrane was glued on the top of the tube next to the electrodes. The polymer film consisted of polyvinyl alcohol (PVA) or methacrylic acid copolymer, type B (Eudragit® S 100, Röhm, Darmstadt, Germany) with 28.6% triethyl citrate (Boehringer Ingelheim, Ingelheim, Germany) as plasticizer. The methacrylic acid copolymer films were drawn with a film applicator coater (Erichsen No. 580034, type A/B, Erichsen, Hemer-Sudwig, Germany) and tempered at 60 °C for 24 h. The thickness of the dried membranes was 19, 24, 32 (methacrylic acid copolymer films) or 56 μm (PVA membranes, industrially manufactured). The thickness was measured using scanning electron microscopy (SCD040 sputter station, Balzers, FL-Balzers; Stereoscan S4, Cambridge Instruments, Cambridge, Great Britain) ($n = 5$). Additionally, before manufacture of the sensor elements the thickness of the films was tested using a film thickness tester (Erichsen No. 497, Erichsen, Hemer-Sudwig, Germany). Only films were used which had a thickness of 19, 24, 32 or 56 μm ±5% relative standard deviation.

To investigate the influence of control membranes on the activation of the sensor elements, the electrodes were connected to a power supply (Voltcraft, Conrad-Electronic, Hirschau, Germany) and an electrical circuit with a resistor element in parallel (5 kΩ), a voltmeter (Delta 350, Mettler Toledo, Gießen, Germany) and a recorder (Servogor, GMC instruments group, Nürnberg, Germany). The reference voltage in the electrical circuit was 5 V. The sensor elements were tested using a dissolution apparatus (Ph. Eur.) (Pharma Test Type PTW, Pharma Test Apparatebau, Hainburg, Germany) with paddles. The sensor elements were immersed into 500 ml of artificial gastric juice (prepared from 1N HCl, Merck, Darmstadt, Germany). After 2 h the liquid was replaced by a phosphate buffer solution pH 6.8 R (phosphates: Merck, Darmstadt, Germany). All liquids had a temperature of 37 ± 5 °C. The testing was stopped after 4 h.

2.2. Capsule-like drug delivery systems with membrane controlled sensor elements

The sensor element was integrated into a capsule-like model drug delivery system. A tube consisting of Plexiglas® with an inner diameter of 6 mm, an outer radius of 10 mm and a length of 22 mm was manufactured. The platinum electrodes and the cellulose depot were fixed in the upper area of the capsule. The electrodes were connected to a gas producing cell (size 3, Simatec, Herzogenbuchsee, Switzerland) via an electrical circuit. A piston, which was manufactured by founding and hardening of liquid polysiloxane, was inserted next to the gas cell. Two hundred microliters of an aqueous solution of 5% prednisolone sodium phosphate (Synopharm, Barsbüttel, Germany) was filled in the bottom of the drug delivery system as drug reservoir. The tube was sealed by a thread with a release orifice at the bottom and by a pH-sensitive membrane, which was glued at the top of the tube. The membrane consisted of methacrylic acid copolymer, type B with 28.6% triethyl citrate as plasticizer. The polymer films were drawn with an Erichsen film applicator coater and tempered at 60 °C for 24 h. The film thickness of the dried membranes was 24 μm.

The release of prednisolone sodium phosphate (10 mg/200 μl) from the capsule-like drug delivery systems was investigated using a dissolution apparatus with paddles. The dissolution medium was water (37 °C, 500 ml) if capsules without membranes were tested ($n = 5$). Drug delivery systems with Eudragit® S100 membranes (film thickness 24 μm) were immersed in artificial gastric juice for 2 h, then the acidic liquid was replaced by phosphate buffer solution pH 6.8 ($n = 5$). The amount of released drug was measured spectrophotometrically (Hitachi Spectrophotometer Model 100-40, Hitachi Ltd., Düsseldorf, Germany) at a wavelength of 247 nm.

3. Results

To get an actively controlled release from drug delivery systems into a specified region of the GI-tract a sensor element was developed (Fig. 1). The sensor element consists of two platinum electrodes, which form a microswitch. After contact with gastrointestinal fluids a small piece of compressed cellulose, which is part of the switch, expands and presses the platinum electrodes together. A polymer membrane protects the microswitch against the gastrointestinal fluids until the release should take place. After decomposition, disintegration or dissolution of the protecting membrane the microswitch is in contact with the gastrointestinal fluid. The electric circuit is switched on and if the sensor element is combined with an active release mechanism (e.g. a drug pump) the release starts.

At first experiments were carried out to characterise the sensor elements. The function of the sensor elements was studied. The influence of control membranes made from water soluble polyvinyl alcohol and from pH sensitive polymethacrylic acid was tested. The switching on of the microswitches was measured via a power supply, an electrical circuit and a voltmeter. A reference voltage of 5 V was applied in the electrical circuit. In

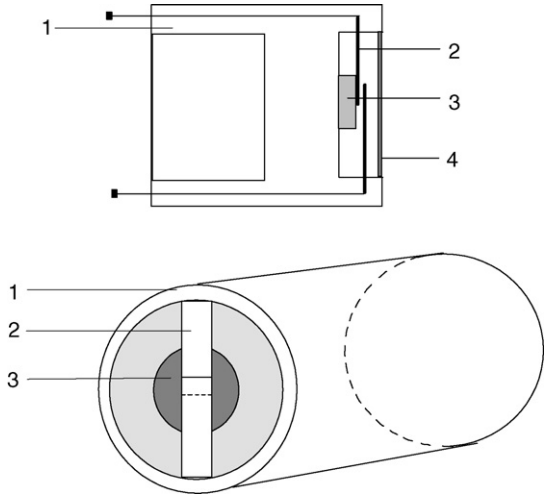

Fig. 1. Construction principle of a sensor element to control day release from capsules. (1) Capsule corpus, (2) platinum electrodes, (3) compressed cellulose and (4) membrane.

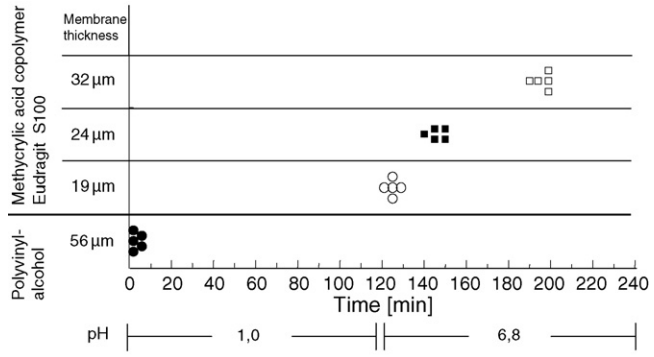

Fig. 2. Membrane thickness and response of sensor elements. (●) Polyvinyl alcohol, 56 μm; (◯) methacrylic acid copolymer, type B, 19 μm; (■) methacrylic acid copolymer, type B, 24 μm and (□) methacrylic acid copolymer, type B, 32 μm.

Fig. 2 the points of time are plotted, when the sensor elements are activated. If water soluble polyvinyl alcohol membranes are part of the sensor elements they are activated within minutes. If gastric resistant membranes prepared from polymethacrylic acid copolymer (Eudragit S 100) are used the microswitches give no signal in artificial gastric juice. After changing the pH from 1.0 to 6.8 the response of the sensor elements depends on the thickness of the membrane, which protects the microswitch. Nineteen-micrometer membranes dissolve within 10 min and at the same time the sensor element is activated. If a 32 μm membrane is used a delay in response of about 80 min following the pH change was measured.

To get an active drug release into a specific site of the GI-tract a capsule was developed, which consists of a sensor element, an electrical circuit and a drug reservoir, which can be filled with a drug solution or suspension. The drug reservoir is emptied by means of a piston which is moved forward by hydrogen gas generated by a commercially available miniature gas producing cell. The gas producing cell looks like a small battery with a diameter of 6 mm. The gas production starts when the positive and negative poles of the gas producing cell are connected via a conducting electrical circuit. To prevent overpressure in the capsule when the reservoir is emptied, a thread inside of the capsule at the end of the reservoir ensures, that the gas is directly transported to the release orifice.

The sensor element is part of the electrical circuit, which controls the start of release. The construction principle of the capsule is shown in Fig. 3.

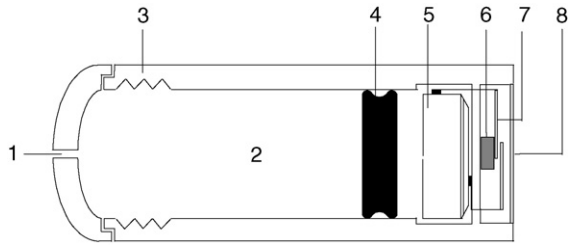

Fig. 3. Schematic diagram of a sensor controlled capsule with gas producing cell. (1) Release orifice, (2) drug reservoir, (3) thread, (4) piston, (5) gas producing cell, (6) compressed cellulose, (7) micro switch and (8) pH-sensitive membrane.

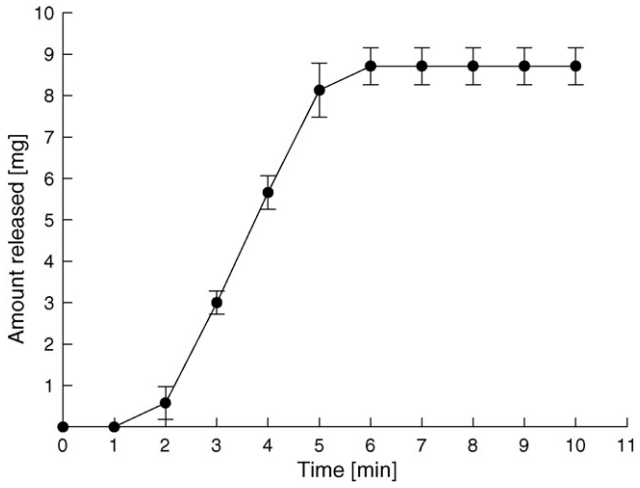

Fig. 4. Release of prednisolone sodium phosphate (10 mg/200 μl) from a sensor-controlled capsule without membrane ($n = 5$, arith. mean ± s).

In Fig. 4 the in vitro drug release from capsules is shown. Different release patterns are obtained if the sensor element is used without a membrane or if a pH sensitive polymethacrylic membrane (Eudragit S 100) is part of the sensor element. The capsule was filled with an aqueous drug solution containing 10 mg prednisolone sodium phosphate in 200 μl. Without a membrane the drug solution is released at once. Nine milligrams of the drug are pumped out of the reservoir. Ten percent of the drug solution remains in the front section of the reservoir. If a 24 μm gastric resistant membrane is part of the sensor element no drug is released during the first two hours in pH 1.0 artificial gastric juice. After two hours the pH was changed to 6.8. Forty minutes later the drug was released from all capsules.

4. Discussion

In the present investigations drug delivery systems were developed, in which the onset of release is controlled by sensor elements. Polymers sensitive to bacterial enzymes or to pH can be used as control membranes. The system was constructed for in vitro experiments. It was the aim of the study to get information about this new construction principle, which in the future may be used to get a targeted release into a specific area of the GI-tract. For human use it is necessary to build up devices, which are biodegradable and which are save from the toxicological point of view.

In small sized drug delivery systems, which exist today, the release of the active substances is controlled by passive processes. Only in a few cases active and energy controlled release mechanisms are used, e.g. in the OROS-systems in which mechanical energy is generated via an osmotic process. Drug delivery systems of the future may use sensors and remote controlled mechanisms to get reproducible drug release kinetics.

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