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International Journal of Pharmaceutics 193 (1999) 57–61

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Pulsed release of nitroglycerin from transdermal drug delivery systems

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Received 14 July 1999; received in revised form 10 August 1999; accepted 2 September 1999

Abstract

To achieve a discontinuous drug delivery to the skin a new actively controlled transdermal system has been developed. The system consists of a tube shaped drug reservoir in combination with an electronic circuit and a gas producing cell. A magnetic switch was used to control the onset of the production of hydrogen gas. The gas was generated with a constant rate. The tube reservoir was filled with a solution of nitroglycerin in propylene glycol. A discontinuous distribution of nitroglycerin in the reservoir is responsible for the pulsed release. 2, 3, 4, or 6 fractions of nitroglycerin solution, which were separated from each other by sections with air, were filled into the tube reservoir. The release studies show that the release patterns directly reflect the number of doses, which were filled into the tube. A lag time of about 60 min was obtained, if the gas production is regulated by a 2.7 kΩ resistor. The drug is released during the pre-programmed time intervals within 6–7 h. Between the time intervals no drug release occurs.

Keywords: Transdermal system; Pulsed release; Nitroglycerin; Tube reservoir; Gas producing cell

1. Introduction

Transdermal drug delivery patches can be classified into two types: membrane controlled reservoir systems and matrix or monolithic systems (Müller and Hildebrand, 1997). The drug release from these devices is mainly controlled by different diffusion processes. Membrane controlled reservoir systems release the drug from a reservoir through a rate-limiting membrane to the surface of the skin. The reservoir is not totally emptied. If the initial diffusion of the drug from the reservoir is used, a nearly constant release rate is obtained for some hours or days (Bonn and Rehe, 1985; Lescure et al., 1989). In matrix systems the drug is embedded in polymer layers. With matrix systems nearly constant drug delivery rates are obtained, too. The release profiles of drugs from these transdermal systems may be influenced by the construction principle of the device, by the interactions of the system with the humidity of the skin and by the thermodynamic activity of the drug substance in the specific drug carrier.

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0378-5173/99/$ - see front matter
PII: S0378-5173(99)00308-7

In the future drug delivery systems in which energy controlled active release mechanisms are used to liberate the drug (Baker, 1987) will become more and more important. Actively controlled drug release at particular moments may be important to adjust the release profiles of the drug to the individual requirements of the patient or to generally optimize drug therapy. It was the aim of the present investigations to develop new transdermal systems with actively controlled drug delivery to the skin.

2. Materials and methods

2.1. Materials and construction of the model dosage form

The drug reservoir of the model dosage form was formed as a spiral from a 160 cm long polytetrafluoroethylene-tube with a inner diameter of 0.3 mm (Fa. Novodirect, D-Kehl, Art.-Nr.: D 39240) and attached to a flat polymer foil using acrylic glue for polytetrafluoroethylene (Fa. Loctite, D-München). The resulting spiral diameter was 4 cm. In the inner region of the spiral a space with a diameter of 0.6 cm was left. In this area the gas producing cell (Fa. Simatec, CH-Herzogenbuchsee, size 3) and the electronic circuit were placed. Gas producing cells are galvanised elements, which are placed in a battery-like housing, consisting of a beaker and a lid with a diameter of 7.8 mm and a height of 3.6 mm. The beaker and the lid represent the two poles of the cell. When the two poles of the cell are connected with a conducting material, the hydrogen gas production starts. In the circuit of the gas producing cell, a SMD-resistor (Fa. Conrad-Electronic, D-Hirschau, 2.7 kΩ) and a magnetic switch (Fa. Hamlin, D-Bad Vilbel, Typ MITI-3) were installed to control the gas production. The electronic elements were connected with conductive glue (Elecolit 325 A + B, Fa. Panasol-Elosol, D-Frankfurt). During the release experiments the magnetic switch was switched on to start the gas production with the help of a miniature permanent magnet. Nitroglycerin was used as a model drug. Nitroglycerin was prepared from 1.5 g nitroglycerin solution (Fa. Merck, D-Darmstadt, 1% in ethanol) by drying at 50°C. A concentration of 67 mg nitroglycerin in 1 ml propylene glycol (Fa. Caelo, D-Hilden) was prepared. The tube reservoir system was filled with the drug solution in varying sections by the help of a Hamilton microliter syringe. The sections between those containing solutions were filled with air. The filling of the tube reservoir was based on the following plan: for release of nitroglycerin at intervals, varying sections of the tube reservoir were filled. A filled section contained a volume of 8 μl. In order to achieve release pattern with two nitroglycerin pulses, two sections of the tube were filled. By separating the two sections with a section containing 134 μl air, an interval without drug release was achieved. In order to have three nitroglycerin pulses, three amount of 8 μl drug solution were separated with 63 μl air filled tube sections. In systems with four or six filled tube sections, the volume of the nitroglycerin is 6 μl in each section. Four filled tube sections were separated by 42 μl air filled sections. 23 μl air filled sections separated the nitroglycerin solution when the tube reservoir contains six sections.

2.2. Release experiments

To reduce the diffusion of the hydrogen from the tube reservoir system during the release experiments the model dosage form was embedded into a polymer layer made from polyester (Fa. Hobby Time, D-Neukirch, poly casting resin). The gas producing cell was connected with the filled tube reservoir using a connection unit, which was made from a part of an injection needle (Fa. Braun, D-Melsungen, Typ: Sterican Luer-Lock G 26). The experiments were conducted at room temperature. The released substance was collected every 15 min in 20 ml phosphate buffer solution pH 6.4 (DAB 1996). The content of nitroglycerin in the fractions was measured by polarography (Polarograph VA 663, Polarecord 626 Fa. Metrohm).

3. Results

In the present investigations new transdermal drug delivery systems were developed. To obtain actively controlled drug release from transdermal patches a small tube shaped drug reservoir in combination with a gas producing cell and an electric circuit were integrated in the system. The application of gas producing cells in small drug delivery devices like capsules was described earlier by our group (Weyel, 1995). A gas producing cell looks like a miniature watch-battery. An electrochemical redox process starts when the poles of the cell are connected by a conductor (Winsel, 1989a,b; Fa. Simatec, 1993). The tube reservoir was filled with a solution of nitroglycerin in propylene glycol. Hydrogen was generated by the gas producing cell to produce a controlled emptying of the drug reservoir. The gas was generated at a constant rate. A defined rate of about 33.5 μl/min was adjusted by a 2.7 kΩ resistor. A tube length of 160 cm was chosen. When the electrical circuit is switched on, the release takes place for 6–7 h. To obtain a pulsed release of nitroglycerin from the reservoir 2, 3, 4, or 6 fractions of the nitroglycerin solution were filled into the tube reservoir. The drug containing sections of the tube were separated from each other by sections filled with air.

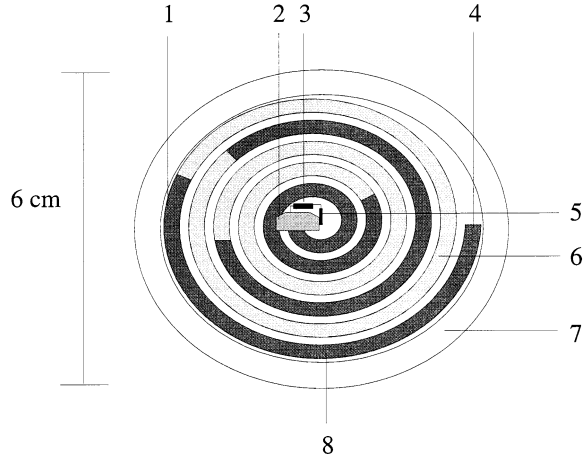

Fig. 1. Schematic diagram of a model dosage form containing a tube reservoir to obtain a pulsed release of drugs. 1: PTFE-tube; 2: gas producing cell; 3: magnetic switch; 4: drug release orifice; 5: resistor; 6: air filled section free of drug; 7: layer of glue and 8: section containing drug substance.

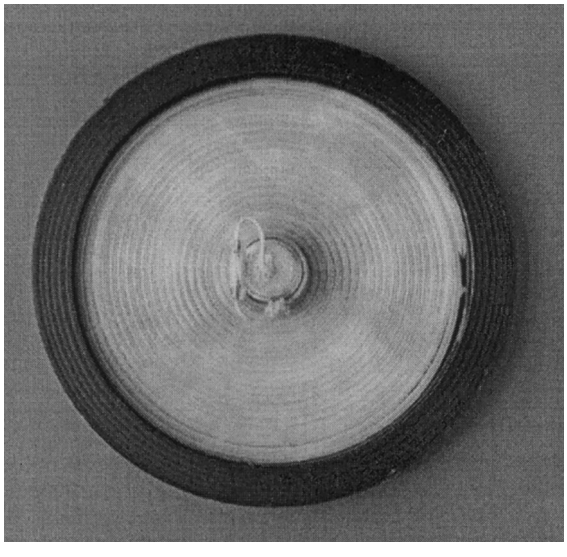

Fig. 2. Photograph of the transdermal tube reservoir system without a backing layer; spiral diameter: 4 cm.

A schematic diagram of the transdermal system is shown in Fig. 1. The poles of the gas producing cell (2) are connected via a resistor (5) and a magnetic switch (3). With the switch, gas production can be started. To start the release process a miniature permanent magnet is attached to the transdermal system. The cell is linked to the tube reservoir (1) via a connection unit. The sections in the tube are each filled with nitroglycerin in propylene glycol (8). In the sections without drug solution (6), air is present. The spiral made from the tube has a diameter of 4 cm. In order to reduce the diffusion of hydrogen gas from the tube during the release process, the tube was embedded in a polymer layer. The generated hydrogen gas empties the tube reservoir in the direction of the release orifice (4). A photograph of the transdermal tube reservoir system without a backing layer is given in Fig. 2.

Fig. 3 shows the results of the drug release studies. The cumulative release of nitroglycerin is plotted against time. Four different systems, filled with two, three, four or six doses of nitroglycerin, were tested. The release patterns directly reflect the number of doses, which were filled into the tube. In each experiment one dose of the nitro-

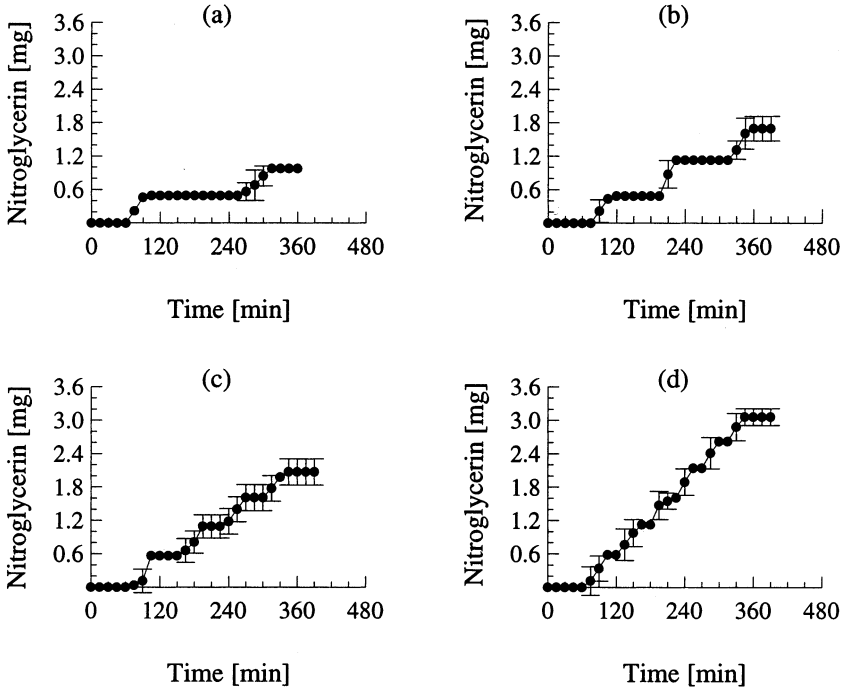

Fig. 3. Pulsed release of nitroglycerin from a tube reservoir system with gas producing cells; $n = 5$; arithmetic mean $\pm$ s. (a) Two filled sections; (b) three filled sections; (c) four filled sections and (d) six filled sections.

glycerin solution is located directly near the release orifice of the tube reservoir. The results of the investigations show that the release of nitroglycerin starts in each case approximately 60 min after the system is turned on, the delay being caused by the lag-time of the electrochemical reaction in the gas producing cell. It is dependent on the electrical resistance of the electrical circuit. If the gas production is regulated by a 2.7 kΩ resistor a lag-time of about 60 min occurs. The results shown in Fig. 3a were obtained, if two sections of the reservoir were filled with nitroglycerin solution (8 μl), separated from each other by 134 μl air. The first dose of approximately 0.5 mg nitroglycerin is released after 90 min. Then the release stops. Drug release starts again after 270 min. The second dose of approximately 0.5 mg is released after 310 min.

The release profile for a tube reservoir containing three filled sections is shown in Fig. 3b. Three doses with a total amount of approximately 1.5 mg nitroglycerin were released within 360 min. Fig. 3c shows the results when four sections of the reservoir were filled with nitroglycerin. Within a total of 345 min, four pulses with approximately 2.1 mg substance are released. Fig. 3d shows the release curve when nitroglycerin is released over 345 min in six intervals.

4. Discussion

The permeation rates of drugs through the skin are different. Nitroglycerin is a drug which has a high permeation rate. For the transdermal route, thus nitroglycerin seems to be an optimal candidate for pulsed skin delivery.

Until now investigations to obtain pulsed drug release from transdermal systems were not very successful, if diffusion controlled membrane or matrix systems for transdermal drug delivery were used (Hardgraft et al., 1990). So it was necessary to develop a new construction principle for transdermal systems. In the present study, model

dosage forms were developed, containing a tube reservoir system combined with a gas producing cell. With the new system, pulsed release of nitroglycerin can be achieved. In our preliminary investigations the reservoir is emptied continuously. The discontinuous distribution of the drug solution in the reservoir is responsible for the pulsed release.

In further studies new techniques for automatic preparation of the system should be investigated. Stability tests will be necessary to show that the distribution of the drug solution in the reservoir system is not effected by the movement of a patient who uses a transdermal system with an integrated tube reservoir. The stability of nitroglycerin in the system should also be investigated.

When hydrogen is used to empty the tube reservoir, the diffusion of the gas through the wall of the tube may influence the release rates. Through embedding the system into a polyester polymer layer, the hydrogen diffusion was reduced.

References

Baker, R., 1987. Controlled Release of Biologically Active Agents. Wiley, New York.

Bonn, R., Rehe, A., 1985. Bioverfügbarkeit-ein Qualitätsmerkmal zur Beurteilung der transdermalen Systeme von Glyceroltrinitrat. Dtsch. Apoth. Ztg. 125, 2073–2077.

Hardgraft, J., Wolff, M., Bonn, R., Cordes, G., 1990. Development of biphasic transdermal nitroglycerin delivery systems. Int. J. Pharm. 64, 187–194.

Lescure, F., Gurny, R., Doelker, E., Augustynski, J., 1989. Utilisation du principe de l'iontophorèse ou de l'électrophorèse pour le control de la libération de substances médicamenteuse. Pharm. Acta Helv. 64, 210–219.

Müller, R.H., Hildebrand, G.E., 1997. Pharmazeutische Technologie: Moderne Arzneiformen. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart.

Produktinformation Gasentwicklungszelle, 1993. Fa. Simatec Industrietechnik, CH-Herzogenbuchsee.

Weyel, S., 1995. Pharmazeutisch-technologische Untersuchungen zur Entwicklung kleindimensionierter Modellarzneiformen mit computergesteuerter Wirkstofffreisetzung. Dissertation, Westfälische Wilhelms-Universität Münster, Germany.

Winsel, A., 1989a. Deutsche Patentschrift DE 3711714 C2.

Winsel, A., 1989b. Gasentwicklungszellen. In: Dechema Monographie, 117, Verlag Chemie, Weinheim, pp. 265–278.