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Electrophoretically controlled dermal or transdermal application systems with electronic indicators

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Summary

The present investigation describes a system for the local application of basic drugs to the skin, using the antihistamine diphenhydramine hydrochloride as an example in which the release of drug from a gel-type carrier is controlled by a weak electric field. In vitro studies of the release of drug showed that for example, through the application of 9 V, the amount of diphenhydramine hydrochloride released from a gel carrier in 5 min can be increased by a factor of 2.5. A newly developed, pencil-shaped application system contains an integrated voltage supply and an electronic indicator to show when the system is in operation. Investigations in 6 subjects of the current flow and electrical resistance of the human body show that the current through the body caused by the drug pencil is about 86 μA.

Introduction

In the past few years, dosage forms for the dermal or transdermal application of drugs have gained increasingly in importance. The release of active ingredient from these drug carriers and the permeation through the skin proceed according to the laws of passive diffusion.

As only a few drugs permeate the skin in therapeutically required amounts, in future drug carrier systems will be developed and used that provide energy for the active release of the drug and under certain conditions, will actually transport the drug into the body across the skin barrier. Electrophoretically controlled application systems are likely to become especially important (Ariura et al., 1982; Spevak et al., 1982). With these drug carriers it is possible to induce the migration of charged substances in the electric field and achieve an active transport of drug.

The rate of migration (vi) of ions in the presence of electrolytes in an electric field is directly proportional to the field strength H and the effective charge (Δe) of a particle and inversely proportional to the radius of the particle ai (which includes the hydrate and ion shell in the calculation) and to the viscosity of the medium in which the particles are moving. The rate of migration is thus given by the following equation:

$$vi = \frac{\Delta e \times H}{6 \times \pi \times ai \times \eta}$$

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The aim of the present investigation was to develop systems for the local application of antihistamines to the skin. These application systems were to be suitable for the short-term treatment of acute skin irritations caused, for example, by insect bites. The duration of use was to be in the region of minutes and be directed towards alleviating the symptoms.

A system designed for only short-term use was planned as the application of electrophoretically controlled releasing drug carriers to the skin for longer periods is only possible to a limited extent, due to the degradation of water and the associated marked shift in pH of the drug carriers (Gröning, 1986). It is particularly important that such devices for use on the skin carry some form of indicator to show when the drug is being released. Therefore during the course of the presence investigations, an attempt was made to develop an electronic indicator for electrophoretically releasing dermal or transdermal systems.

Materials and Methods

Power supply: electronically stabilised electrical supply unit, type SNT 7000 (Buehler Elektronik, Baden-Baden, F.R.G.). Voltmeter/Ammeter: universal measuring apparatus, type DMM 3020 (BEWA, Holzkirchen, F.R.G.). Spectrophotometer: double-beam spectrophotometer, type UV-210A (Shimadzu, Kyoto, Japan).

Composition of the gel carriers. Diphenhydramine gel: 230 mg diphenhydramine hydrochloride, 345 mg agar agar DAB 6, 4.6 g glycerol ph.Eur. (all 3 Merck, F.R.G.) to 23.0 g purified water. Drug-free gel: 345 mg agar-agar DAB 6 to 23.0 g purified water.

Manufacture of the gel carriers. The constituents of the gel carriers are homogeneously mixed together and dissolved with heating. After cooling to about 40°C, 2.3 g portions are poured into circular plastic containers of 20 mm internal diameter and a depth of 4 mm. The upper surface of the gel carriers are in contact with thin aluminium electrodes which could be polarised via a supply line either as anode or cathode.

Composition and preparation of the acceptor mediums. The acceptor medium used in the release experiments consists of an aqueous 1.5% agar-agar hydrogel. The gel is prepared by warming and then is poured into a suitable vessel to form a block with a height of 5 cm.

Methods for the release experiments. In each experiment one gel carrier containing a drug is arranged as anode (+) with a drug-free gel carrier as cathode (−) placed on the acceptor medium at a distance of 10 mm. Each gel carrier was subjected to a weight of 200 G. The voltage is supplied from an electronically stabilised supply apparatus. The amount of diphenhydramine hydrochloride released was measured spectrophotometrically at 230 nm. The amount of diphenhydramine in the acceptor medium and in the gel carriers was determined after dissolving them in 50 ml of a buffer solution pH 7.2 (34 g KH_2PO_4, 34 g NaCl, 189 ml NaOH, purified water to 5000 ml).

Measurement of current flow and body resistance in man. The current flow and resistance in the human body was measured between an aluminium electrode (aluminium tube 10 mm diameter) that was held with the thumb, index finger and middle finger of the right hand and an agar gel carrier (anode) on the inner surface of the left wrist. The voltage supply was provided by 3 lithium batteries each of 3 V (National, Type BR435, Matsushta Electronic Industrial Co., Japan). The current was measured with an ammeter.

Structure of the application system. The drug pencil consists of a circular aluminium cartridge with an external diameter of 14 mm and an internal diameter of 11 mm. The aluminium case is 92 mm long and is connected as cathode (Fig. 2). At its lower end, the drug pencil has a plastic isolator 15 mm long, with an external diameter of 11 mm and an internal diameter of 8 mm that holds the gel. The latter has a length of 20 mm and is connected as anode. The gel is prevented from drying out by an aluminium protective cap. There is a 4 mm diameter hole bored in the area of the electronic circuitry to hold the LED. The 3 lithium batteries placed one on top of the other can be changed via a screw cap at the top end of the aluminium case. The batteries and the entire circuitry, are isolated from the aluminium case by foil.

Results and Discussion

Model experiments on the release of diphenhydramine hydrochloride

In the present attempt to develop an electrophoretic dermal or transdermal application system for basic drugs, the antihistamine diphenhydramine HCl was used as an example. The drug substance was incorporated in a concentration of 20 mg/g in an agar gel carrier that was polarised as anode against an agar cathode. Both gel carriers were fixed in a model experiment to the surface of an acceptor medium, that also consisted of an agar gel. Fig. 1 shows the effects of applied potential on the amount of diphenhydramine released in 5 min from a gel carrier polarised as anode. Compared to the control, the amount of drug released into the acceptor medium can be increased, by for example, the application of 9 V, by about 2.5 times. The results of the investigations thus show that by using low voltages of 3–9 V, a controlled release of active ingredient from drug carriers can be achieved. For these preliminary release experiments, only a model system was used with which the basic behavior of electrophoretically releasing dosage forms can be characterised. The functional control was provided by an ammeter and voltmeters.

Development of a new application system

It is desirable that an electrophoretically controlled system for the dermal or transdermal application of drugs by patients is fitted with an integrated voltage supply and a indicator device to show that the system is being used properly.

The application system shown in Fig. 2 was developed to meet these requirements. The basic drug is present in dissolved form in an agar gel carrier. The latter is connected as anode. The voltage is supplied by 3 lithium batteries with a total voltage of 9 V. On use, the drug-containing gel carrier is brought into contact with the area of skin to be treated. The electrical circuit that is required to form the electric field is made via the hand of the patient who holds the application system at the cathode, through the patient's body and the gel carrier at the point of application. The current flow and the body's resistance under the conditions of use were measured in 6 subjects and

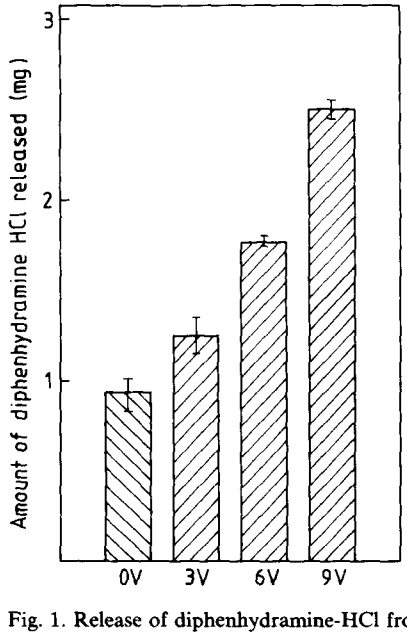

Fig. 1. Release of diphenhydramine-HCl from agar gel carriers on short-term use (5 min, amount in acceptor phase, $n = 5$, $\pm$ S.E.M.).

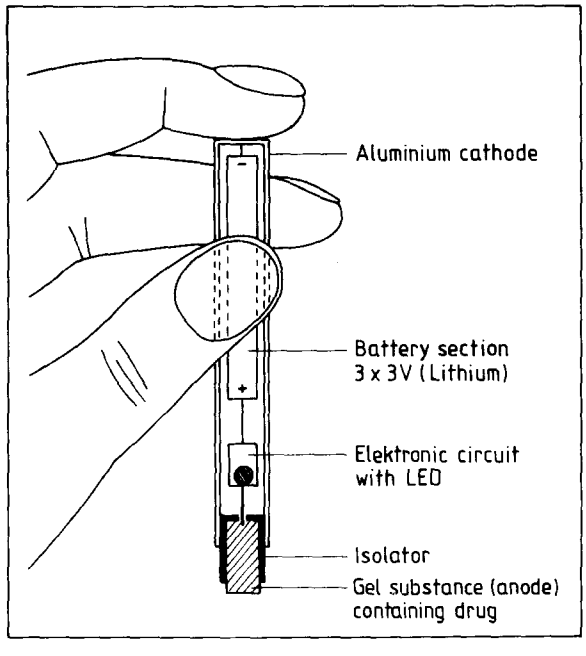

Fig. 2. Schematic representation of a dermal or transdermal application system.

TABLE 1

Current flow and body resistance in humans from the right to the left arm

Subject no.	I [μA]	R [kΩ]
1	78	115
2	90	100
3	50	180
4	67	134
5	153	58
6	80	112
$\bar{x}$	86.3	116.5

9 V, Al cathode, gel anode.

the results are given in Table 1. The mean current flow was 86 μA and the mean electrical resistance of the body was measured as 116 kΩ. The degree of variation in the results reflected, among other things, the high variability in skin resistance among the 6 subjects. The investigations of current flow show that during the use of the application system, a closed circuit is formed with an electric field in which drug transport can occur.

Development of an electronic indicator

As a functional check, the application system contains an electronic display which is shown in Fig. 2 and depicted as a circuit diagram in Fig. 3. A diode lights up as soon as a current flow occurs when the system is in use. As is illustrated by the circuit diagram in Fig. 3, the voltage drop at resistor R_3 in the circuit is used to indicate the flow of current. The voltage drop on use causes, via an operation amplifier, the lighting up of the diode LED_1. The resistor R_3 only slightly impairs the flow of current during use, since its influence is small compared to the body's resistance. The electronic circuit takes up an area of about 1 cm^2.

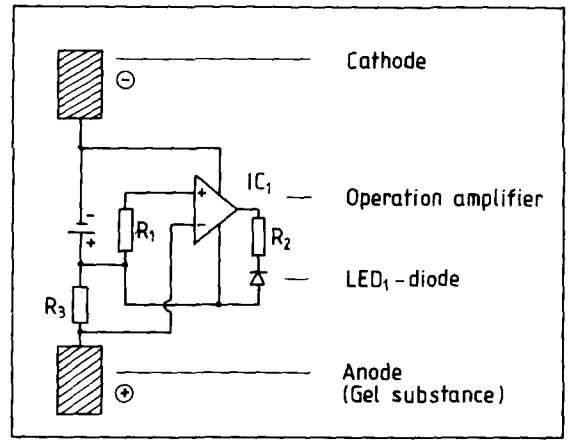

Fig. 3. Circuit diagram of a dermal or transdermal system with electronic indicator. $R_1 = 47$ kΩ; $R_2 = 1$ kΩ; $R_3 = 3.9$ kΩ; IC_1 = TL061, selected; LED_1 = CQV-10-4/99. All resistors microtype, 1/16 W, $\pm 5\%$ tolerance.

It is thus easily accommodated in the pencil-shaped drug application system.

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