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Hydrogel Patches for Transdermal Drug Delivery; In-vivo Water Exchange and Skin Compatibility

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Abstract—Hydrogel patches based on water swellable polyacrylates have been developed for long-term transdermal drug delivery. Two properties, relevant to the performance of hydrogel patches in-vivo have been investigated in humans over five days. These were: (i) the kinetics of water exchange between the skin and the patches; (ii) the skin compatibility of the patches. It was found that initially there was a gradually increasing uptake of water from the skin by the patches, but after about 20 h the water exchange followed a regular fluctuating pattern, peaking once a day and once a night. The skin compatibility of the patches was satisfactory, in that no redness or pustulation was noticed throughout the five days. This was most likely due to the capability of the patches to exchange water with the skin.

Transdermal drug delivery systems (TDS) constitute a major advance in sustained drug release; they have been designed for controlled transdermal drug delivery with the intention of maintaining constant plasma levels (Shaw 1982; Fara 1983; Coeleweij & Junginger 1984). TDS have a number of advantages over oral or rectal dosage forms in that they are easy to self administer, they allow for efficient therapy with low dosing frequency (since a single dose may suffice for extended periods of several days) potential side effects are suppressed, constant plasma levels of the drug can be obtained, and hepatic first-pass metabolism is avoided. However, the administration of drugs with TDS as they are currently being used, may have drawbacks, two of which are the unwanted side effects in the skin due to long-term occlusion and, in some cases, the undesirable pharmacological consequences of sustained drug delivery at low plasma levels. Concerning occlusion effects, practically all TDS marketed are based on hydrophobic polymer matrices, and are therefore occlusive. Long-term (4–7 days) application of these systems implies prolonged occlusion of a single area of skin, and hence may evoke a number of unwanted side effects. These may include: clogging of sweat ducts, resulting in the sweat retention syndrome (Hurkmans et al 1985; Boddé et al 1987); accumulation of potentially harmful bacteria (Aly et al 1978; Hurkmans et al 1985) and an increased risk of allergic and/or irritant reactions elicited by potential allergens or irritants in the TDS (Wester & Maibach 1985; Boddé et al 1989). By using non-occlusive (e.g. water swellable) materials for TDS these side effects may be overcome, at least partially (Hurkmans et al 1985).

In our view it is possible that some skin irritation problems associated with transdermal delivery could be avoidable and may well depend on the design of the transdermal dosage form, especially on the choice of the basic material.

The present study deals with hydrogels as ground material for transdermal patches and, more specifically, with hydrogel-skin interactions in-vivo.

Generally, hydrogels can be described as two-component systems, one component being a hydrophilic polymer forming a three-dimensional network and the other component being water. Hydrogels are widely studied biomaterials and materials for the preparation of sustained release drug dosage forms (Roorda et al 1986). Their soft consistency and their high biocompatibility in a number of applications make them promising candidates for preventing the side-effects mentioned earlier.

A wide range of applications of hydrogels has been described, among them contact lenses, burn wound dressings and haemodialysis membranes (Coeleweij & Junginger 1984). The transport properties of hydrogels make them useful as drug delivery systems. Investigations have been made on dosage forms such as cylinders, tablets and spheres. A different application is their use in transdermal therapeutic systems. As has been shown by Hurkmans et al (1985), hydrogels have a high skin compatibility, probably due to water exchange with the skin, and may therefore be suitable for skin compliant TDS.

The aim of this study was to quantify the water exchange between hydrogels and the skin in-vivo, and to verify the skin compatibility of hydrogel patches.

Materials and Methods

Hydrogel patches were designed as shown in Fig. 1. At first an aqueous suspension of Eudragit E 30 D (Röhm Pharma, Weiterstadt, West Germany) was cast on aluminium foil, followed by evaporation of the water at room temperature (20°C) for 48 h. After removal of the foil the hydrogel film was cut into small pieces and 2·69 g of hydrogel was dissolved in 40 mL of acetone p.A. (J.T. Baker Chemicals, Deventer, the Netherlands). This solution was cast on top of a sheet of aluminium foil (total surface area 660·5 cm^2) to serve as a primer for backing attachment, followed by evaporation of the solvent at room temperature for 48 h; on top of the film thus obtained, a solution was cast, containing 16·25 g of Eudragit RL 100 (Röhm Pharma, Weiterstadt, West Germany) and 5·4 g of poly(oxyethylene)$_{10}$-oleylether (Brij 96, ICI Atlas Chemie, Essen, West Germany) in 60 mL of ethanol 96% p.A. (J.T. Baker Chemicals, Deventer, the Netherlands), followed by evaporation of the solvent at room temperature. The surfactant Brij 96 served as a plasticizer for the hydrogel. The film thus obtained contained 0·0246 g of Eudragit RL 100 and 0·008 g of Brij 96 per cm^2

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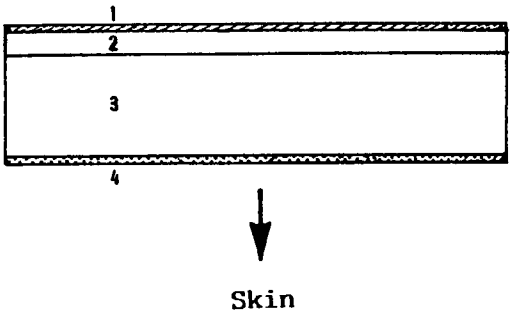

FIG. 1. Schematic cross-section through a hydrogel patch; 1. backing layer; 2. Eudragit E30d, 3. Eudragit RL100+Brij 96; 4. adhesive layer.

surface area. Finally, an acrylic based water permeable adhesive layer (S 695, Avery International, Turnhout, Belgium) was attached and small circular patches of 12 mm diameter were excised. The total thickness of the patches was approximately 350 μm, of which 50 μm consisted of the aluminium foil and Eudragit E 30 D. Thicker patches were not flexible enough in wearing and showed insufficient skin adhesion. Thinner patches had a reduced water uptake capacity. The hydrogel patches were not loaded with any drug throughout the experiment. The hydrogels are copolymers of acrylic acid and poly(meth)-acrylic esters, chosen because of their high flexibility and because they have been approved by the FDA. The difference between Eudragit E 30 D and Eudragit RL 100 is that the latter has a small content of quaternary ammonium groups and swells faster than the former.

Design of the experiment

Eight volunteers (5 males and 3 females) each received 39 hydrogel patches on the abdominal skin at 0900 h on the first day. After application on the skin the patches were secured with Fixomull stretch adhesive tape (BDF, Hamburg, West Germany). The volunteers were asked to refrain from excessive physical activity and to avoid wetting treated skin areas throughout the experiment. The patches were sampled (using a pair of tweezers) at various intervals covering a total period of 100 h. Upon sampling, patches were immediately stored in preweighed glass crimp top vials sealed with polyethylene snap caps (Chrompack International, Middelburg, The Netherlands) until further analysis. Sampling of patches (one at a time per volunteer) occurred every 2 h between 0 and 14, 22 and 38, 46 and 62, 70 and 86 and 94 and 100 h after application. No samples were taken between 2300 and 0700 h. After each sampling, the treated skin sites were inspected for erythema and/or folliculitis.

Analytical procedures

The water content of the patches was determined as follows: the vials containing the patches were weighed within one day of sampling on a mechanical microbalance (E. Mettler, Zürich, Switzerland). The vials with the patches, but without the caps were then dried in an oven (Homef, Beun-de-Ronde, Amsterdam, the Netherlands) for 48 h at 95°C; the vials were then closed and weighed again. The relative water content of the patches was then calculated. To verify the surfactant content of the patches, the amount of Brij 96 was determined inside an initial (0 h), an intermediate (52 h) and a final (100 h) sample of each volunteer. The analytical procedure for the Brij 96 determination was a modification of the method described in the Dutch Pharmacopoeia (1980): The vial containing the sample was first thoroughly cleaned on the outside, then smashed with a hammer and introduced into a 50 mL flask with a ground-glass stopper previously rinsed with glacial acetic acid p.A. (J.T. Baker Chemicals, Deventer, the Netherlands); the sample was then dissolved in 2 mL of chloroform p.A. (J.T. Baker Chemicals, Denventer, the Netherlands). Subsequently, 1·00 mL of an 8·00 gL^{-1} iodine bromide (E. Merck, Schuchardt, West Germany) solution was added slowly. The flask was closed and kept in the dark for 30 min, and frequently shaken. Then, 2·00 mL of a 25% w/v solution of potassium iodide (ACF Chemiefarma NV, Maarssen, the Netherlands) was added, together with 10 mL of distilled water. Finally this mixture was titrated with 0·006 M sodium thiosulphate, shaking vigorously, until the yellow colour almost vanished. 0·5 mL of a 10·0 gL^{-1} starch solution was then added. The titration was continued by dropwise addition of the 0·006 M sodium thiosulphate until complete discolouration. A blank test was carried out under the same conditions. The amounts of Brij 96 were quantified using a calibration curve covering a range between 1 and 10 mg.

Statistics

The following statistical procedures have been used: the results have been analysed with a one way analysis of variance program on an Apple IIe computer (A2 Devices, Alameda, California USA). The results were also subjected to a Newman-Keuls test (Grimm 1973).

Results and Discussion

Water exchange kinetics

Analysis of the patches indicated no significant change in surfactant (Brij 96) content of the patches over time; hence correction of the percentage water content values for changes in the surfactant content was omitted. The results are shown in Fig. 2. The most important results of a statistical test of the data are listed in Table 1. Major sources of error probably are: the intersite and inter-individual variability in water exchange behaviour of the skin, variability in patch swellability and adhesivity, and analytical errors. Of these the latter two sources were controlled as much as possible. Fig. 2 indicates that the water content in the patches gradually increases over the first 20 h, and subsequently fluctuates. Statistically significant differences occurred only between 0 and 22 h, 2 and 22 h, 4 and 22 h, 0 and 24 h, 2 and 24 h, 4 and 24 h, 46 and 76 h, and 70 and 76 h after application. However, the water content of the patches followed a surprisingly regular pattern in that it reached a maximum once a day and once a night. This implies that the fluctuations although not all significant, cannot be identified as "noise". The fact that from the second day the mean water content fluctuated about a plateau (of about 16 percent weight) suggests that a dynamic steady state was reached, in which the uptake of water by the patches from the skin was almost compensated for by the loss of water from the patch

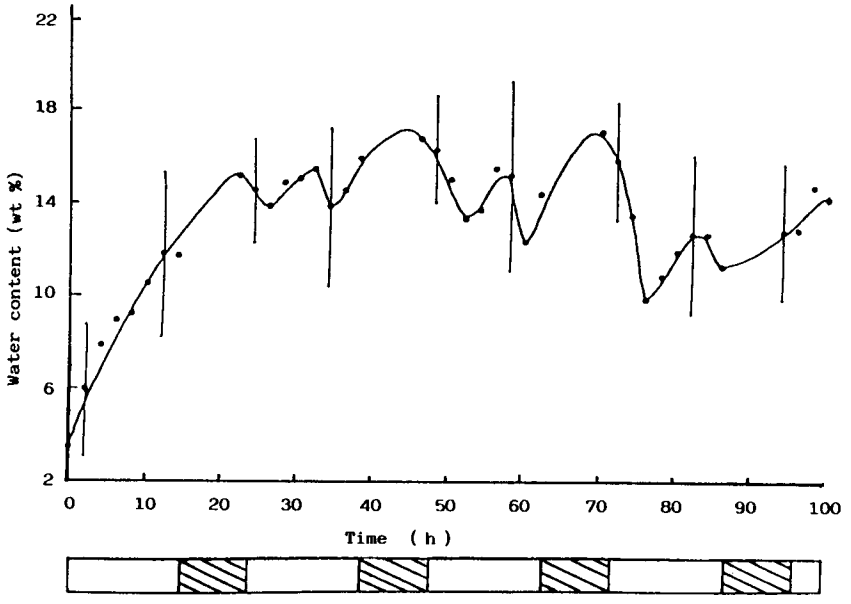

FIG. 2. Water content of hydrogel patches (with s.d. n = 8) as a function of duration of skin contact in-vivo. Open blocks 0900–2400 h. Shaded blocks 2400→0900 h.

Table 1. Newman-Keuls multiple range test of data (all differences listed are significant for $\alpha = 0{\cdot}05$).

Hypothesis (time (h))	Q	P	v
0 = 22	9·26	31	273
2 = 22	7·31	30	273
4 = 22	5·82	29	273
0 = 24	8·78	25	273
2 = 24	6·83	24	273
4 = 24	5·33	23	273
70 = 76	5·80	34	273
46 = 76	5·49	33	273

$Q = \text{Studentized range} = \frac{(\bar{x}_{max} - \bar{x}_{min})}{s}$

P = Maximum number of treatments

v = Degrees of Freedom = n(m − 1)

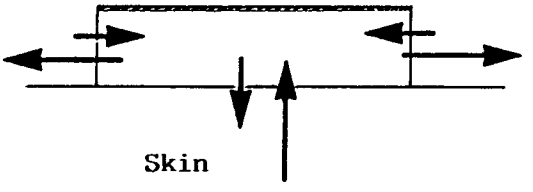

FIG. 3. Directions of water transport through a hydrogel patch applied to the human skin.

edges to the environment; in other words: the skin "breathes" through the patches (Fig. 3). The "pulses" are probably caused by a combination of (a) fluctuations in sweat production and transepidermal water loss, (b) fluctuations in the relative humidity of the surroundings, and (c) fluctuations in the osmotic pressure difference between the patches and the skin. The maximization of the water content between 1700 and 1900 h on each day may be explained by an increased physical activity of the volunteers as they return home from their work. In the literature circadian rhythms in blood pressure have been described by Moore Ede (1967), indicating that there is a minimum blood pressure in the early morning hours and a maximum in the evening. Whether there is a relationship between blood pressure and sweat secretion was not investigated, but seems likely. Also, some papers have been published about fluctuations in body temperature as a function of time (Conroy & Mills 1970), indicating that the body temperature is slightly higher during the night than during the day. We found an increase in water content of the patches during all four nights and we assume this is the result of the warm environment in which the human body is maintained during sleep. Under those circumstances, the major mechanism whereby water is accumulated at the skin surface is most likely thermoregulatory sweating, a form of sensible perspiration. This type of sweating occurs especially on the upper trunk and face (Rook & Wilkinson 1979). Furthermore, a close, positive correlation has also been established between skin temperature and transepidermal water (insensible perspiration) by Thiele (1974).

To our knowledge, transdermal drug delivery as a function of the water exchange between the skin and a patch has not previously been investigated for any drug. For example, it is still unknown to what extent hydrogel patches can influence the drug permeability of stratum corneum. The lack of occlusivity of hydrogel patches might have to be compensated for by the incorporation of penetration enhancers. Another question is whether fluctuating water exchange between a transdermal patch and the skin can provoke pulsed delivery of the drug.

Skin compatibility

The skin compatibility of the patches was satisfactory, since no erythema, or pustulation on the treated skin sites was observed throughout the experiment. None of the volunteers

reported subjective signs of irritation caused by the patches; some noticed a minor itch, most likely caused by the (Fixomull) protective tape. This finding compares with earlier findings using hydrogel patches (Hurkmans et al 1985; Boddé et al 1986). In an extensive in-vivo study on 78 patients, both the polyacrylate adhesive and a combination of the polyacrylate adhesive with an Eudragit E 30 D based patch were dermatologically tested (Boddé et al 1986). Readings after 48 and 72 h, showed complete absence of allergic or primary irritant reactions in all patients. It seems likely that the high skin compatibility of the investigated patches is strongly connected with the observed water exchange, i.e. with their capacity to allow the skin to "breathe" (see also Hurkmans et al 1985).

In conclusion a non-irritant, water swellable and water permeable hydrogel patch has been manufactured, which may be useful for developing skin compatible TDS.

References

Aly, R., Shirley, C., Cunico, B., Maibach, H. I. (1978) Effect of prolonged occlusion on the microbial flora, pH, carbon dioxide and transepidermal water loss on human skin. J. Invest. Dermatol. 71: 378–381

Boddé H. E., Kranenburg, T., Driel, L. M. J. van. (1986) Hydrogels for transdermal derug delivery: skin compliance and water exchange in vivo. Pharm. Weekbl. Sci. Ed. 18: 96.

Boddé, H. E., Verhoeven, J., Driel, L. M. J. van. (1989) The skin compliance of transdermal drug delivery systems. CRC Criticial Reviews in Therapeutic Drug Carrier Systems; In Press

Coeleweij, M. B. M., Junginger, H. E. (1984) Transdermale therapeutische systemen. Pharm. Weekbl. 119: 321–325

Conroy, R. T. W. L., Mills, J. N. (1970) Human circadian rhythms, J&A Churchill Ltd., London

Fara, J. W. (1983), Short- and Longterm transdermal drug delivery systems. Abstract, Int. Conf. of Drug Delivery Systems. RS First Inc., Paris

Grimm, H. (1973), Biostatistics in Pharmacology. In: Delaunois A. L. (ed) International Encyclopedia of Pharmacology and Therapy. Vol. I. Pergamon Press, Oxford, pp 675–716

Hurkmans, J. F. G. M., Boddé, H. E., Driel, L. M. J. van, Doorne, H. van, Junginger, H. E. (1985) Skin irritation caused by transdermal drug delivery systems during long-term (5 days) application. Br. J. Dermatol. 112: 461–467

Moore Ede, M. C. (1967) Circadian rhythms of drug effectiveness and toxicity. Clin. Pharmacol. Ther, 14 (6): 925–935

Dutch Pharmacopoeia, 9th ed. (1980) Staatsuitgeverij, The Hague, 173

Rook, A., Wilkinson, D. S. (1979) in: Ebling, F. J. G. (ed) Textbook of Dermatology, 3rd ed. Blackwell Scientific Publications, Oxford, UK, pp 1678–1680

Roorda, W. E., Boddé, H. E., Boer, A. G. de, Bouwstra, J. A., Junginger, H. E. (1986). Synthetic hydrogels as drug delivery systems. Pharm. Weekbl. Sci. Ed. 8: 165–189

Shaw, J. E. (1982) Transdermal Therapeutic Systems. In: Brandau, R., Lippold, B. H. (eds) Dermal and Transdermal Absorption. Wissenschaftliche Verlagsgesellschaft, Stuttgart, pp 171–175

Thiele, F. A. J. (1974) Measurements on the surface of the skin. Ph.D. Thesis, Nijmegen, the Netherlands

Wester, R. C., Maibach, H. I. (1985) Perspectives of dermal and transdermal drug delivery. in: Breimer, D. D., Speiser, P. (ed) Topics in Pharmaceutical Sciences, Elsevier Science Publishers, 359–364