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Report

Transdermal Controlled Administration of Indomethacin. I. Enhancement of Skin Permeability

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It was observed experimentally that indomethacin delivered in an aqueous suspension has a greater skin permeation rate in an ionized form than in a nonionized form. In this investigation, a matrix-type transdermal drug delivery system was developed to deliver indomethacin molecules in nonionized form. The skin permeation rate of nonionized indomethacin molecules from this system could be substantially improved by incorporating skin permeation enhancers, such as straight-chained alkanols, alkanoic acids, and esters. These enhancers form microreservoirs with indomethacin in the lipophilic silicone polymer matrix. By varying the alkyl chain length of alkanol, alkanoic acid, and its ester, the concentration of permeation enhancer, or the loading dose of indomethacin in the polymer matrix, the skin permeation rate of nonionized indomethacin molecules can be enhanced by as much as 30 times, which is almost sevenfold greater than the rate for ionized indomethacin molecules.

KEY WORDS: indomethacin; transdermal administration; enhanced skin permeability.

INTRODUCTION

Oral administration is currently the principal route of administration for indomethacin, a highly effective antiinflammatory agent in the treatment of rheumatoid arthritis (1). The clinical use of indomethacin, however, is often limited because of its potential to cause some adverse reactions such as irritation and ulceration of the gastrointestinal mucosa, particularly at high dose levels (2). The high initial plasma concentration of the drug after its oral administration appears to be responsible for the side effects (3). To minimize the adverse effects observed, an indomethacin ointment was developed for percutaneous administration (4). A sustained plasma level was achieved without yielding the high initial peak concentration (4) often observed with oral administration. In addition, indomethacin has an unusual property of attaining a higher concentration in the synovial fluid than in the general circulation at steady state (5). It was therefore attempted to develop a rate-controlled transdermal delivery system for the controlled administration of indomethacin which will be applied on the joints in the treatment of rheumatoid arthritis.

The first in this series of investigations intends to report the results of in vitro studies on the transdermal permeation of indomethacin from a matrix diffusion-controlled drug delivery system. The enhancement of the skin permeation rate of indomethacin by the use of skin permeation enhancers, such as alkanol, alkanoic acid, and its esters, is also disclosed. Additionally, the transdermal permeation of ionized and nonionized forms of indomethacin is discussed.

EXPERIMENTAL

Materials. The following chemicals were used as obtained: indomethacin, *n*-hexanol, *n*-octanol, *n*-decyl alcohol, lauryl alcohol, myristyl alcohol, *n*-butyric acid, *n*-caproic acid, *n*-caprylic acid, *n*-capric acid, *n*-lauric acid, *n*-myristic acid, caprylic acid ethyl ester, caprylic acid propyl ester, caprylic acid butyl ester, capric acid propyl ester, myristic acid methyl ester, myristic acid ethyl ester, myristic acid isopropyl ester, and palmitic acid propyl ester (obtained from Sigma Chemical Company, St. Louis, Mo.), polyethylene glycol (PEG) 400, methanol, acetonitrile, sodium phosphate dibasic, and potassium phosphate monobasic (obtained from Fisher Scientific Company, Fair Lawn, N.J.), silicone elastomer 382, and silicone medical fluid 360 (obtained from Dow Corning Corporation, Midland, Mich.).

High-performance liquid chromatographic (HPLC)-grade water was freshly prepared in the laboratory (by Nanopure system, Sybron/Barnstead, Boston, Mass.). Hairless male mice (HRS/J strain, 5–7 weeks old) were obtained biweekly (from Jackson Laboratories, Bar Harbor, Maine).

HPLC Assay. A high-performance liquid chromatographic system equipped with a reciprocating piston pump (Model 6000A, Waters Associates, Milford, Mass.), an injector (Model U6K, Waters Associates), a programmable variable wavelength UV/vis detector (Model 783, Kratos Analytical Instruments, Ramsey, N.J.) operating at a wavelength of 260 nm, a reversed-phase μ-Bondapak C_{18} column (15 cm × 3.9-mm I.D.), and a strip-chart recorder (Series 5000, Fisher Recordall, Houston Instrument, Austin, Tex.) were used in this study.

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The mobile phase was a 40:60 (v/v) mixture of acetonitrile and 1/15 *M* phosphate buffer (pH 6.0). The flow rate was 1.5 ml/min, with the column temperature ambient. Under these conditions, a well-defined indomethacin peak appeared at the retention time of 2.4 min (chromatographic capacity factor, $k' = 1$).

The detection limit of this HPLC method is 0.05 μg/ml, based on a peak height–noise ratio of at least 5.

A calibration curve was constructed using a series of standard solutions of known indomethacin concentration and the peak height method was employed to determine the concentration (μg/ml) of indomethacin in the sample solution.

Fabrication of Devices. Indomethacin-containing matrix-type transdermal delivery devices (TDD) were prepared by first dispersing indomethacin crystals in silicone fluid 360, in which an enhancer may be added, and then mixing well with silicone elastomer 382. After mixing thoroughly, a drop of catalyst M was added with continuous stirring. Following the deaeration under a vacuum, the mixture was transferred to a device maker and then cured in an oven at 60°C for 2 hr.

Drug Release Studies. Two units of indomethacin-releasing TDDs were sandwiched back to back between the two half-cells of a hydrodynamically well-calibrated skin permeation system reported previously (6), which was thermostated at 37°C by a circulating water bath. An aliquot (3.5 ml) of a 30% aqueous PEG 400 solution was delivered to each half-cell and the starhead magnets were rotated at 600 rpm by a specially designed synchronous driving unit. Samples were withdrawn at the appropriate time intervals and assayed for indomethacin concentration by HPLC method. To maintain the sink condition, the whole cell content was withdrawn and then replaced with an equal volume of prewarmed (37°C) elution solution (drug-free) at each sampling time. The amount of drug withdrawn was corrected in the calculation of the cumulative amount released.

Skin Permeation Studies. The hairless mouse was sacrificed just before an *in vitro* skin permeation experiment by snapping the spinal cord at the neck. A square area of the full-thickness abdominal skin was surgically removed and its dermal surface was carefully cleaned to remove extra fatty tissues. The skin samples obtained from this procedure were quite uniform and no other treatment was needed to clean them. Two pieces of the skin were then laid evenly on a pair of the half-cells with their dermis facing the solution compartment. A TDD was applied onto each skin surface with its indomethacin-releasing surface in intimate contact with the stratum corneum. The two half-cells were then clamped together. An aliquot (3.5 ml) of a 30% aqueous PEG 400 solution was filled into each half-cell as the drug elution medium. Samples (50 μl) were withdrawn at predetermined times and assayed for indomethacin by the HPLC method.

Effect of pH on Skin Permeation of Indomethacin. An excess amount of indomethacin crystals was suspended in a series of phosphate buffer solutions, each with a pH of 2.5, 3.5, 4.5, 5.5, 6.5, or 7.5. The suspensions were equilibrated in a shaking water bath at 37°C for 24 hr and then introduced into the donor half-cell of the permeation system with the skin mounted between two half-cells. An aliquot (3.5 ml) of a 30% aqueous PEG 400 solution was then filled into the receptor half-cell. The same experimental procedure outlined above in Skin Permeation Studies was then followed.

RESULTS AND DISCUSSION

Effect of pH on Skin Permeation of Indomethacin. Figure 1 displays the skin permeation of indomethacin from indomethacin suspensions of various pH values. As the pH value of the suspensions increased from 2.5 (indomethacin has a pK_a of 4.5 and therefore is predominantly in nonionized form at this pH value) to 4.5 (at which 50% of indomethacin is in ionized form), the permeation rate of indomethacin remained low and increased only slightly. When the solution pH increased beyond 4.5, an exponential increase in the skin permeation rate was observed. Also shown in Fig. 1 is the solubility versus pH profile for indomethacin. The similar trend observed for both profiles implies that the increase in the skin permeation rate of indomethacin at higher pH levels may have been due to the increase in the aqueous solubility of indomethacin. Since indomethacin is mainly in ionized form at higher pH levels, the results suggest that indomethacin anions are skin permeable, and the higher the aqueous solubility and the concentration of indomethacin are, the greater is its skin permeation rate. This observation is rather different from the skin permeation characteristics of most drugs, in which neutral species are more lipophilic in nature and are often reported to have a greater skin permeability than the ionic form, and this could explain the results recently reported for an *in vivo* study (4).

Kinetics of Controlled Indomethacin Release. In this study, the aim was to deliver indomethacin as neutral molecules at a controlled rate of delivery. To achieve this objective, a matrix-type TDD system was developed by dispersing indomethacin crystals in the lipophilic silicone elastomer. A typical release profile of indomethacin from such a TDD system is shown in Fig. 2. A linear relationship between the cumulative amount of indomethacin released (Q) and the square root of time ($t^{1/2}$) was obtained after a steady state was reached (with a correlation coefficient of 0.995), indicating that the mechanism of drug release follows the

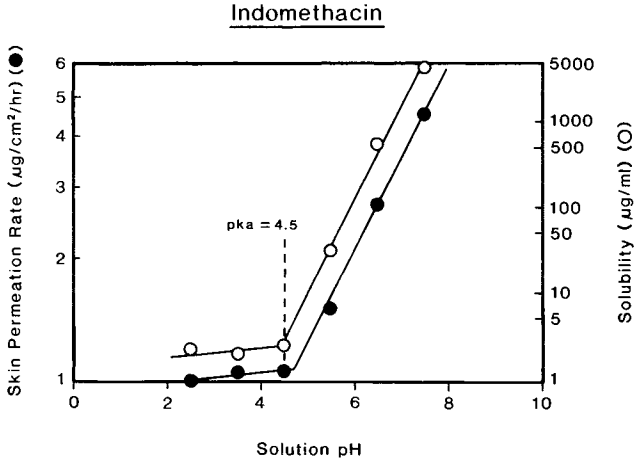

Fig. 1. pH dependence of the aqueous solubility of indomethacin and its skin permeation rate across hairless mouse skin from a drug suspension.

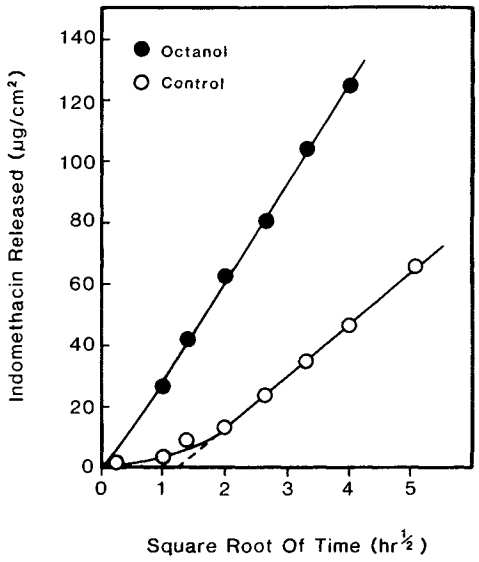

Fig. 2. Effect of octanol on the release profile of indomethacin from the matrix-type TDD system.

matrix diffusion-controlled process as described by the classical Higuchi relation (7,8).

Incorporation of octanol as the dispersing medium for indomethacin in the silicone polymer matrix increased the release flux ($Q/t^{1/2}$) of indomethacin.

Kinetics of Skin Permeation and Pemeability Enhancement. A good linear relationship between the cumulative amount of indomethacin permeated and time was observed (Fig. 3), indicating that skin permeation of indomethacin is kinetically controlled by the stratum corneum (9,10).

When 10% of octanol, capric acid, or isopropyl myristate was incorporated into the TDD as the skin permeation enhancer, the skin permeation profile of indomethacin was substantially increased. The results are tabulated in Table I.

The data in Table I confirm that as indomethacin is delivered from the lipophilic silicone elastomer matrix (in nonionized form), the lowest rate of skin permeation (0.94 ± 0.07 μg/cm²/hr) is obtained, which is in agreement with the permeation rate vs pH profile reported earlier. However, with the incorporation of octanol, capric acid, or isopropyl myristate as the skin permeation enhancer for indomethacin, the skin permeation rate of indomethacin can be enhanced by as much as ninefold (8.45 vs 0.94 μg/cm²/hr). The extent of enhancement in the skin permeation rate of indomethacin resulting from the incorporation of octanol and capric acid in the silicone polymer matrix is almost twice as great as that observed from delivering indomethacin from the solution at pH 7.5 (8.23–8.45 vs 4.48 μg/cm²/hr). At this pH, indomethacin solutes should all exist in ionized form.

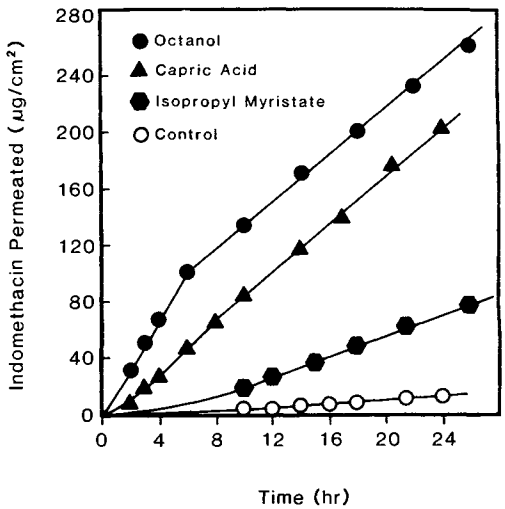

Fig. 3. Enhancing effect of various representative skin permeation enhancers on the transdermal permeation profile of indomethacin released from the TDD system.

Table I. Skin Permeation Rate of Indomethacin and Effect of Skin Permeation Enhancers

Enhancer	Permeation rate (μg/cm²/hr ± SD)[a]	Enhancement factor[b]
Control	0.94 ± 0.07	1.00
Octanol	8.45 ± 0.56	8.99
Capric acid	8.23 ± 1.51	8.75
Isopropyl myristate	3.59 ± 0.14	3.82

[a] $N = 3$.

[b] Enhancement factor = [(skin permeation rate) enhancer/(skin permeation rate) control].

It was also noticed that the skin permeation profile of indomethacin with octanol as a skin permeation enhancer showed a shift in permeation profile at the 6-hr point. Several reports in the literature have revealed that alkanols are capable of penetrating the skin (11,12). The results in Fig. 3 seem to suggest that, in the initial stage of skin permeation, octanol could act as a carrier to promote the skin permeation of indomethacin, and hence a relatively high rate of permeation was obtained in this stage. After 6 hr of skin permeation the concentration of octanol on the skin surface is reduced, but the skin's barrier properties are also overcome; thus the rate of skin permeation of indomethacin shifts to a steady-state level.

Effects of Alkyl Chain Length on Skin Permeation Rate. To gain some understanding of the mechanism of skin permeation, the effect of variation in the alkyl chain length of alkanol, alkanoic acid, and its propyl ester on the skin permeation rate of indomethacin was investigated. It was found that as the alkyl chain length in the alkanols and alkanoic acids increases, the transdermal permeation rate of indomethacin is increased initially, reaches a maximum rate, and then drops as the number of methylene groups in the alkyl chain is greater than six to eight. This phenomenon is very similar to the observation reported earlier for progesterone delivered transdermally from a multilaminate TDD system (13).

Skin has been considered as a bi- or multiphase tissue, with one phase (or a collection of several phases) being constituted of a hydrophilic protein gel and another phase (or a collection of phases) being made of a lipophilic fatty matrix (10,11). The low molecular weight alkanols ($N \leq 6$) may act as a solubilizer which enhances the solubility of indomethacin in the fatty matrix of the stratum corneum, thus pro-

moting the permeation of indomethacin molecules. After the maximum permeability is reached, the skin permeation of indomethacin molecules becomes limited by the rate of diffusion across the hydrophilic viable epidermis and/or dermis, resulting in a reduction in the skin permeability. The trends noted above are also followed by alkanoic acids, with the maximum skin permeation rate attained at $N = 8$. The esterification of alkanoic acids, however, seems to reduce the effectiveness of alkanoic acids in promoting the skin permeation of indomethacin. The same phenomena were also observed in the enhanced permeation of progesterone (13) and nitroglycerin (14).

Effects of Ester Chain Length on Skin Permeation Rate. The effect of the alkyl chain length in the ester of alkanoic acid on the skin permeation rate of indomethacin was also evaluated. The observed results indicate that the effectiveness of fatty acid esters in enhancing the skin permeation of indomethacin also depends upon the alkyl chain length of the fatty acid itself. An increase in the number of CH_2 groups, from methyl to propyl, in the esters of myristic acid yielded a proportional increase in the skin permeation rate of indomethacin, whereas a slight decrease in skin permeation was observed as the alkyl chain length in the esters of capric acid increased.

Effect of Enhancer Concentration on Skin Permeation. The results in Fig. 3 and Table I suggest that the maximum skin permeation rate of indomethacin is achieved with octanol as a permeation enhancer. Using octanol as an example, the effect of the enhancer concentration in the TDD system on the enhancement of the skin permeation rate of indomethacin was studied. The data in Fig. 4 suggest that on increasing the concentration of octanol in the TDD system, a significant increase in the permeation rate of indomethacin occurs. The maximum rate of skin permeation (~29 $\mu g/cm^2/hr$) was observed at 16% (w/w) of octanol, which is almost sevenfold greater than the skin permeation rate of indomethacin anion at pH 7.5 (Fig. 1).

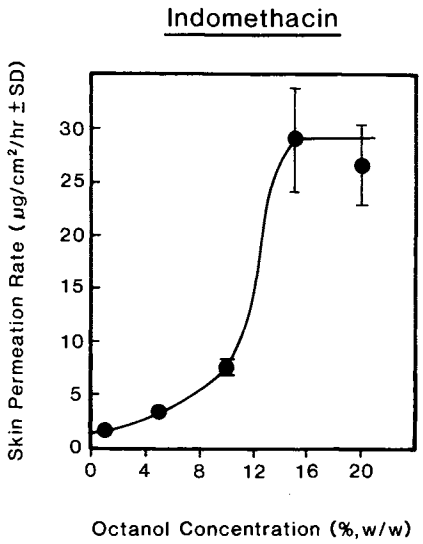

Fig. 4. Dependence of the transdermal permeation rate (mean ± SD) of indomethacin on the concentration of octanol, as the skin permeation enhancer, in the TDD system.

Effect of Drug Loading Dose on Skin Permeation. The effect of the loading dose of indomethacin on its skin permeation rate was also investigated. The results suggest that the skin permeation rate of indomethacin increases rapidly at a low loading level (5–8%) and then reaches a plateau level as drug loading increases to 10% (w/w) and beyond.

In conclusion, indomethacin can be delivered in nonionized form by releasing it from a lipophilic silicone polymer matrix and its skin permeation rate can be substantially enhanced by incorporating straight-chained alkanols or alkanoic acids to form microreservoirs with indomethacin in the polymer matrix. The rate of skin permeation can be regulated by controlling the number of methylene groups in the alkyl chain of alkanol as well as in alkanoic acid and its ester used, the concentration of a permeation enhancer, and the loading dose of indomethacin incorporated in the TDD system.

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