Effect of physicochemical parameters on skin permeability of antihypertensive

Bijaya Ghosh* & L. Harivardhan Reddy
Department of Pharmaceutical Technology, V.L. College of Pharmacy, Raichur 584 101, India

Received 5 June 2000; revised 23 January 2001

Studies were carried out to establish a correlation of skin permeability with physicochemical parameters using five antihypertensive drugs. In vitro skin permeation was carried out in vertical type diffusion cells. When steady-state fluxes of the drugs were correlated with physicochemical properties, good correlation was obtained with the reciprocal of melting point. Weak correlation was obtained with partition coefficient, molecular weight and solubility. However skin permeability versus solubility profiles revealed an interesting trend. The initial permeation rates of the poorly water soluble drugs, prazosin hydrochloride and reserpine were higher than their steady-state fluxes and moderately water soluble drug atenolol showed more or less similar permeation throughout the entire span of the study. This trend changed gradually and reversed completely in the highly water soluble drug diltiazem hydrochloride. The study suggests that drug derivatives of low melting point and good aqueous solubility could be favorable candidates for transdermal delivery.

Since transdermal dosage forms offer the advantages of intravenous infusion many drugs have been studied for the purpose of transdermal delivery. To assess the feasibility of skin permeation, initial experiments are carried out using animal and cadaver skin. This system is expensive and cumbersome as large number of experiments are needed to be performed due to extensive biovariation of skin properties in both humans and animals.

Research is also going on to predict and understand skin permeability from the viewpoint of physicochemical parameters of the drug substance. In the present study, we have attempted to examine the skin permeation profile of a number of potent antihypertensive agents and correlated the steady-state fluxes with the physicochemical properties, viz. solubility, partition coefficient, melting point and molecular weight. Of the candidate drugs used in the present investigation, propranolol hydrochloride has been widely studied. Maitani et al. have also predicted good skin permeability of this drug by calculating its theoretical partition coefficient. The permeation studies on diltiazem hydrochloride, prazosin hydrochloride and atenolol were also attempted previously.

Materials and Methods

Drugs used were, reserpine (Novartis Mumbai); prazosin hydrochloride (Sun Pharmaceutical Industries, Gujarat); atenolol (Parke-Davies Ltd., Hyderabad), propranolol hydrochloride (Cipla Ltd., Mumbai); diltiazem hydrochloride (Micro Labs., Bangalore). All the drugs were received as contributory samples. Chemicals used include, methanol, ethanol (Qualigens, Mumbai); octanol (Rolex Laboratories, Mumbai); physiological saline (Core Healthcare, Gujrat); gentamicin sulphate (Nicholas Piramal India Ltd., Mumbai). Swiss albino mice were purchased from National Institute of Nutrition, Hyderabad, India.

Solubility measurements

The solubility determination was carried out by the method of Okumara et al. An excess amount of the drug was taken and dissolved in measured amount of distilled water in a glass vial to get a saturated solution. The system was kept at rest for 24 hr at 37°C to attain the attainment of equilibrium with the undissolved drug particles. The supernatant was filtered and assayed spectrophotometrically (Hitachi U-2000, Japan) at the suitable wavelengths.

Partition coefficient determination

The octanol-water partition coefficient of the drugs was determined by the method described by Wells. Ten ml of octanol was added to equal volume of aqueous solution of the drug in a separating funnel. The system was kept for 24 hr at 37°C with intermittent shaking. Finally, the aqueous layer was separated, clarified by centrifugation and assayed.

Melting point determination

Melting point of the drugs was determined in a
melting point apparatus Veego (Veego Scientific Devices, Mumbai, India).

**Skin permeation experiments**

The *in vitro* diffusion experiment of drugs was carried out using 6-8 week old female Swiss albino mice (*Mus musculus*). Vertical type diffusion cell (Neutron Scientific, Calcutta) having a downstream volume of 20 ml was used. To avoid accidental scratching of stratum corneum skin was used as such without removing hair. The excised abdominal skin was mounted on the diffusion cell with stratum corneum facing the donor compartment. The receiver compartment was filled with 20 ml of normal saline containing 0.016% gentamicin sulphate to preserve the skin from deterioration. 3 ml of aqueous drug suspension was placed in the donor compartment to maintain constant chemical potential. The temperature was maintained at 37°C. The sample solution was withdrawn at regular intervals and assayed.

**Target flux**

Target flux of the drugs was calculated using the available pharmacokinetic data utilizing the formula of Kim and Chien:

\[
F = \frac{CSS \cdot C(t) \cdot BW}{A}
\]

Where A, F and BW are the surface area of transdermal delivery device, the desired steady-state permeation rate through the skin and the body weight of the subject, respectively. C(t) and CSS are the total clearance and effective plasma concentration respectively. The target permeation rate was calculated assuming the surface area of transdermal delivery device as 10 cm² and body weight of the patient as 60 kg.

**Data analysis**

The cumulative amount of the drugs permeated per unit skin surface area was plotted against time and the slope of the linear portion of the plot was estimated as the steady-state flux (Jss)\(^9\). The permeability coefficient was calculated as,

\[
Kp = \frac{Jss}{Cv}
\]

Where Cv is the total donor concentration of the solute.

**Results and Discussion**

**Diffusivity of the drugs through mice skin**

The permeation profiles of the drugs through mice skin are shown in Figs 1 and 2. Drugs having good water solubility (propranolol hydrochloride, atenolol and diltiazem hydrochloride) showed significantly greater permeation in comparison to poorly water soluble reserpine and prazosin hydrochloride.

**Relationships between skin permeability and physicochemical properties of drugs**

The contribution of physicochemical parameters towards the skin permeability were evaluated (Figs 3-6 and Tables 1-2). Weak correlation was found between the steady-state flux and molecular wt (\(R = -0.64\)), partition coefficient (\(R = -0.54\)) and solubility (\(R = 0.51\)) of the drugs. Also, when log of the steady-state fluxes were plotted with log partition coefficients, no significant correlation was found (\(R = -0.3\)).

The best correlation (\(R = 0.84\)) was found when reciprocal of the melting point was plotted against steady-state flux (Fig 6). Similar observation is also reported by Guy *et al*\(^11\). Since melting point is a measure of the cohesive strength of the drug molecules, it appears that drugs having low intermolecular attraction can move more freely through the stratum corneum. In Fig 7, initial and
steady-state fluxes of the drugs were depicted with increasing order of aqueous solubility. It was noticed that the first hour flux of the poorly water soluble drugs were higher than their steady-state flux. However, with the increase in water solubility, this tendency of showing higher permeation in the initial

Table 2—Desired skin permeation rate (Target flux) calculated from pharmacokinetic data compared with achieved steady-state flux.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Desired plasma Concentration (C)</th>
<th>Clearance (Cl) ml.min⁻¹ kg⁻¹</th>
<th>Target flux µg. cm⁻² hr⁻¹</th>
<th>Steady-state flux µg. cm⁻² hr⁻¹ ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reserpine</td>
<td>6.7 ± 2.9 ng/ml</td>
<td>3.0 ± 0.3</td>
<td>7.2</td>
<td>10.31 ± 4.30</td>
</tr>
<tr>
<td>Prazosin hydrochloride</td>
<td>0.1 µg/ml- 1.0µg/ml</td>
<td>2.0 ± 0.2</td>
<td>360.0</td>
<td>321.44 ± 48.88</td>
</tr>
<tr>
<td>Atenolol</td>
<td>20 ng/ml</td>
<td>16 ± 5</td>
<td>115.2</td>
<td>175.43 ± 94.81</td>
</tr>
<tr>
<td>Propranolol hydrochloride</td>
<td>40 ng/ml**</td>
<td>12 ± 4</td>
<td>172.8</td>
<td>273.04 ± 127.49</td>
</tr>
</tbody>
</table>

*The value was taken from the reference (12)
**The value was taken from the reference (13)
All other values appear in reference (8)

Fig.1 — Permeation of reserpine (■-■) and prazosin hydrochloride (●-●) from the aqueous suspension through the full thickness excised skin of Swiss albino mice. Each data point represents mean ± SE of three animals.

Fig.2 — In vitro permeation profiles of atenolol (●-●), propranolol hydrochloride (△-△) and diltiazem hydrochloride (■-■) through full thickness excised mice skin. In case of diltiazem hydrochloride and propranolol hydrochloride, each data point represents mean ± SE of three experiments, which in case of atenolol, the values are mean ± SE of four experiments.
Fig. 3 — Relationship between skin permeability and solubility of the drugs. The abbreviations used are, RP = reserpine, PH = prazosin hydrochloride, AT = atenolol, PRP = propranolol hydrochloride and DTH = diltiazem hydrochloride. The values are plotted in the increasing order of solubility, but not to scale.

Fig. 4 — Relationship between skin permeability and octanol/water partition coefficient of the drugs. The abbreviations used are, RP = reserpine, PH = prazosin hydrochloride, AT = atenolol, PRP = propranolol hydrochloride and DTH = diltiazem hydrochloride. The values are plotted in the increasing order of partition coefficients, but not to scale.

Fig. 5 — Relationship between skin permeability and molecular weight of the drugs. The abbreviations used are, RP = reserpine, PH = prazosin hydrochloride, AT = atenolol, PRP = propranolol hydrochloride and DTH = diltiazem hydrochloride. The values are plotted in the increasing order of molecular weight, but not to scale.

Fig. 6 — Relationship between skin permeability and reciprocal of melting point of the drugs. The abbreviations used are, RP = reserpine, PH = prazosin hydrochloride, AT = atenolol, PRP = propranolol hydrochloride and DTH = diltiazem hydrochloride. The values are plotted in the increasing order of melting point, but not to scale.

hours decreased. In case of propranolol hydrochloride there was no significant difference ($P > 0.1$) between the first-hour flux and steady-state flux and highly water soluble drug diltiazem hydrochloride showed much less ($P < 0.05$) first-hour permeation than its steady-state flux.

It is reported that, drugs with low water solubility face difficulty in getting partitioned towards more hydrophilic viable epidermis and form reservoir in the lipid-rich intermediate layers of the skin. Hence, it is likely that once this reservoir is formed, the relatively static and concentrated layer of drug had given effect similar to a stagnant boundary layer.
This study suggests that to facilitate transdermal delivery, synthetic drug analogs may be devised having lower melting point and optimum water solubility.

Acknowledgement

The work was supported by S.B.S.(P.G) Institute of Bio-Medical Sciences & Research (Dehradun, India) and V.L. College of Pharmacy, Raichur. The authors are also thankful to Dr. M. K. Chattopadhyay, C.C.M.B., Hyderabad, for his constant co-operation and help.

References


