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COMMUNICATIONS

Influence of Electrical Factors on In Vitro Iontophoretic Delivery of Timolol Maleate

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ABSTRACT

The in vitro iontophoretic delivery of timolol maleate (TM) was carried out using a modified two-chambered, horizontal diffusion cell. The effect of various electrical factors on iontophoretic permeation of drug was analyzed. The iontophoretic permeation of TM through human cadaver skin was more greatly enhanced than the passive permeation. The increase in current intensity linearly increased the permeation of drug. The sine wave form showed the highest permeation than other wave forms used. Pulsed mode iontophoresis seems to be more efficient than constant current drug permeation through skin.

INTRODUCTION

Timolol maleate is a nonselective β-adrenergic blocking drug used in the treatment of hypertension, myocardial infarction, angina pectoris, and other cardiovascular disorders. TM is subjected to an extensive, highly variable hepatic first-pass metabolism and causes gastric trauma after oral administration. To maintain the drug concentration in the therapeutic window the dosing frequency and quantity of drug is increased, which may lead to undesirable gastrointestinal disorders and other systemic side effects.

The transdermal delivery of TM seems to be the ideal route of drug administration with narrow therapeutic index, a short biological half-life (2.5–4.0 hr), and potent activity at a low dose that bypasses the hepatic metabolism and allows slow but controlled delivery. The transdermal delivery of TM is very poor due to its hydrophilic nature and complete ionization (99.9%) at skin pH. To overcome this problem, iontophoresis has been attempted to enhance permeation and deliver the drug as per the requirement through skin.

The present work deals with the effect of iontophoresis and electrical factors on drug permeation through skin.

EXPERIMENTAL

Chemicals and Instruments

Timolol maleate (Cadila Antibiotics Limited, India), silver wire, silver chloride (Aldrich Chemical Company, USA), citric acid, disodium hydrogen phosphate, so-

dium chloride (E. Merk, India), 15 MHz dual-beam oscilloscope, function generator, pulse generator (Pacific Electronics, India), and Shimadzu 150 UV spectrophotometer (Japan) were used.

Permeation Apparatus

A modified two-chambered, horizontal diffusion cell (1) with 9.0 ml capacity was used to perform the drug permeation studies. Ag/AgCl electrodes were prepared (2) and positioned like a four-probe electode system (3) through the small holes of rubber caps of cells. The polarity of electrodes in a cell was chosen so that transport of the drug from donor to receptor cell was facilitated. A small hole of the cap also allowed for the sample to be withdrawn from the receptor cell. The counter and reference electrodes were positioned at a fixed distance of approximately 2.0 cm and approximately 2.0 mm from the skin respectively.

In Vitro Iontophoresis

Full thickness human cadaver skin was prepared as reported earlier (2) and sandwiched between the o-rings of diffusion cells in such a way that the stratum corneum side of the skin faced the donor cell. The area of the skin exposed to the receiving cell was 0.785 cm^2. The donor cell contained 10 mg/ml drug solution in 0.6 M McIlvine buffer (4), pH 8.0, whereas the receptor cell contained only buffer. The tightly clamped cells with electrodes were immersed in a water bath at 37 ± 1°C and the stirring of buffers (60 rev min^{-1}) was maintained constant using a magnetic stirrer. The electrodes of diffusion cells were connected to the function generator/pulse generator and oscilloscope powered by the main supply to emit current. The effect of wave forms and duty cycles on permeation studies was carried out at 0.2 mA current. The intensity of current was maintained constant throughout the experiment. Samples were withdrawn from the receptor cell at preset time intervals for 200 min and the drug was analyzed spectrophotometrically (5) at 294 nm. The passive permeation study was also peformed in a similar way.

RESULTS AND DISCUSSION

The drug permeation studies were described by Fick's law and calculated as cumulative percent drug permeated per cm^2 and expressed as mean ± standard deviation (S.D.) of three assays. Passive permeation showed a 10 min lag period and followed a zero-order permeation rate of 3.0×10^{-3} (S.D. ± 0.08×10^{-3}) percent cm^{-2} min^{-1}. The iontophoresis enhances drug permeation through skin in comparison to passive and directly proportional to the current intensity (Fig. 1). It follows the equation $Ri = fi.i$, where Ri is the perme-

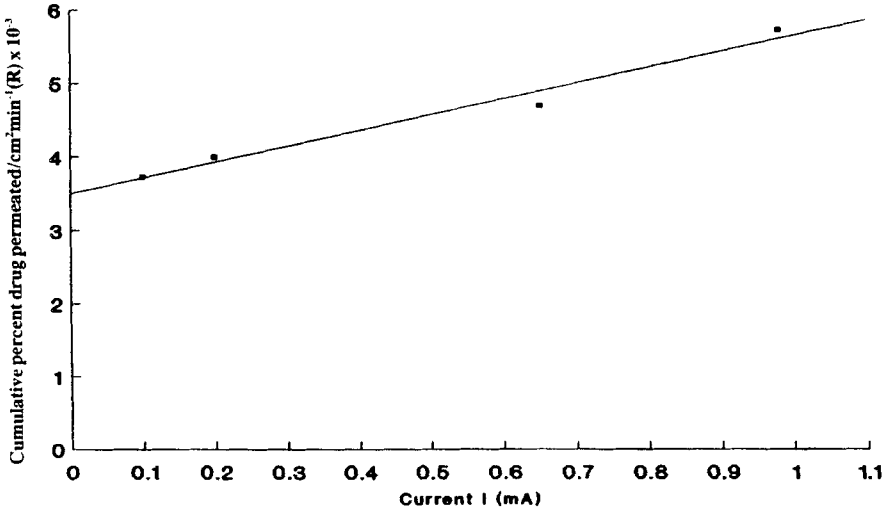

Figure 1. The relationship between the cumulative percent drug permeation rate (r) and current intensity (i).

ation rate of the drug during iontophoresis, i is the current intensity, and fi is the iontophoretic constant for a drug. The value of the constant (fi) is important because it determines the current intensity for the required drug permeation rate, which was found to be 2.13×10^{-3} (S.D. $\pm$ 0.06×10^{-3}) percent cm^{-2} min^{-1} mA^{-1}.

The influence of wave form on the drug permeability through skin was optimized among sine, square, and trapezoidal wave forms at 2 KHz frequency and 1:1 on/off ratio. The highest permeation was recorded to be $1.00 \pm 0.20\%$ cm^{-2} with sine wave (Fig. 2). Liu et al. (6) also found similar results for delivery of insulin in diabetic hairless rats.

The probable mechanism of higher permeation of drug through skin with the application of sine wave is due to the pattern of wave. The current intensity in square wave quickly reaches to peak and is retained for a length of time before falling to zero; whereas in triangular wave, the intensity of current slowly attains the peak and falls to zero without staying at peak. But in the case of sine wave, the current intensity slowly attains the peak and falls down to zero after staying for a time at peak that is less than square wave and more than triangular wave. This pattern of the sine wave may favor the optimum time for polarization/depolarization of the skin to transport the Timolol cations from donor to receptor cell.

The effect of pulse current was studied at 2KHz frequency using 0.2 mA current. The increase in drug permeation from 0.73 ± 0.20 to 1.16 ± 0.19 percent cm^{-2} was recorded with increase in duty cycle from 40% to 80% (Figure 3). This result is in good agreement with the report of insulin delivery in diabetic rats (6). The efficiency of iontophoretic drug permeability was compared between constant and pulse current iontophoresis. The drug permeation 0.87 ± 0.13 and 0.79 ± 0.15 percent cm^{-2} was noted with pulsed and constant current respectively, which indicates the higher efficiency with pulse current (Figure 4).

The pulse current iontophoresis does not develop skin polarization potential against the applied current, thus increasing the efficiency of iontophoretic permeation of drugs. It also protects the skin from the risks of electrical burn, redness, and irritation by prolonged exposure of current.

CONCLUSION

The present studies concluded that the iontophoresis enhanced drug permeation through skin is passive. The intensity of current is linearly correlated to the increase in drug permeation and dependent on the wave form. Sine waves have the highest permeation capacity with an

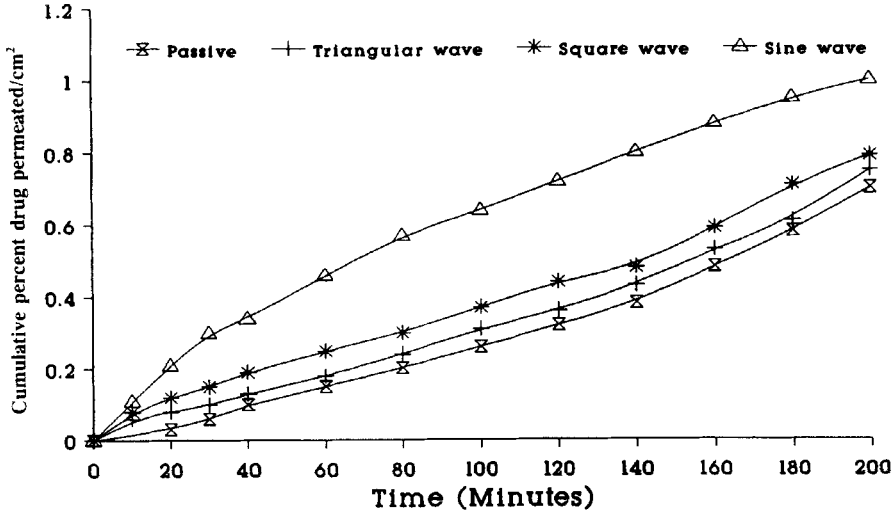

Figure 2. Effect of wave form on permeability of timolol maleate through human cadaver skin.

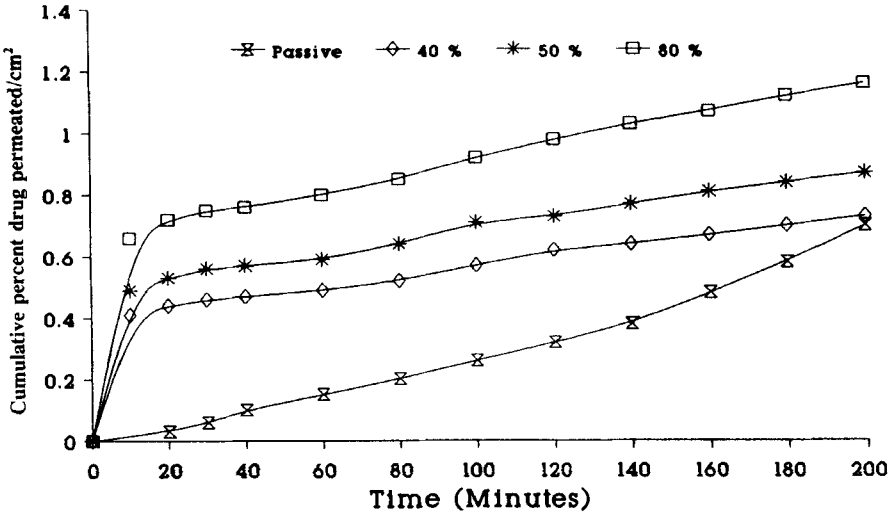

Figure 3. Effect of duty cycle on the the permeability of timolol maleate through human cadaver skin.

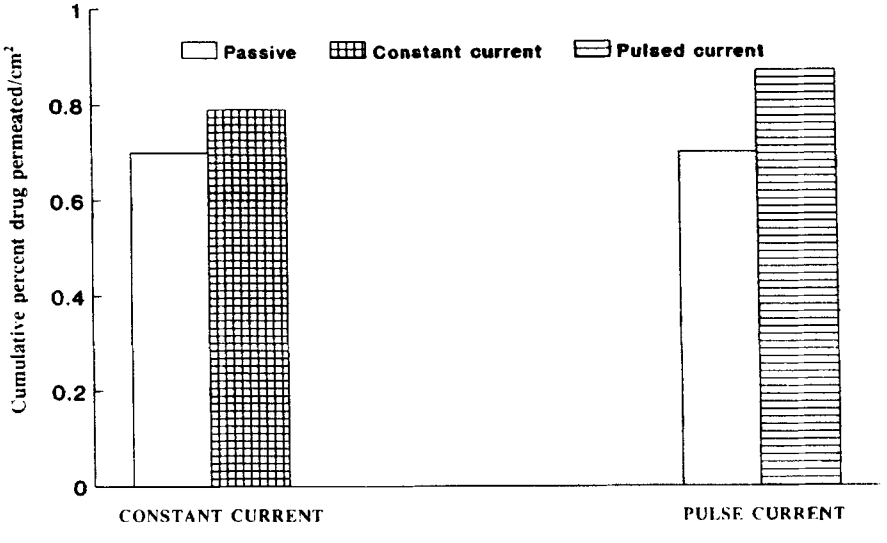

Figure 4. Effect of mode of current on permeability of timolol maleate through human cadaver skin.

increase in duty cycle. The pulse current is more efficient than constant current TM permeation. In order to optimize the iontophoretic drug permeation through skin, more extensive investigations are necessary on various aspects of iontophoretic drug delivery.

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