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Transdermal iontophoretic delivery of methylphenidate HCl in vitro

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Abstract

Methylphenidate is prescribed orally for Attention Deficit Disorder in children and adults, and for narcolepsy patients. Methylphenidate has a short plasma half-life (1–2 h) and thus needs to be frequently administered for effective therapy. Such therapy has limitations in terms of patient compliance, particularly in young children. For such reasons, the development of a transdermal dosage form of methylphenidate may be useful. This study was undertaken to evaluate the passive and electrically assisted transport (iontophoresis) of methylphenidate from aqueous methylphenidate hydrochloride solutions across excised human skin. A maximum flux of 12.0 μg/(cm^2 h) of protonated methylphenidate was estimated from the passive transport data at pH 3.5. Iontophoresis significantly enhanced protonated methylphenidate transport as compared with passive delivery. From the present experiments, the efficiency of iontophoretic delivery of methylphenidate was approximately 700 μg/(mA h). Based on in vitro skin flux data, the daily dose of 15–40 mg methylphenidate can be achieved using a current density of 0.5 mA/cm^2 and a minimum transport area of 2–5 cm^2 for 24-h application, or an area of 4–10 cm^2 for 12-h (daytime) application. From methylphenidate skin flux values, methylphenidate mobility of 2.2×10^{-4} cm^2/(V s) was estimated, which compares reasonably with its free solution mobility of 6.6×10^{-4} cm^2/(V s).

Keywords: Iontophoresis; Methylphenidate

1. Introduction

Methylphenidate is a mild central nervous system stimulant used in the treatment of Attention Deficit Disorders (ADD) and narcolepsy. It is a Schedule II controlled substance. Methylphenidate is available as conventional tablets for oral administration (Ritalin®, Ritalin®-SR is also available as sustained-release tablets). Average daily oral dose is 20–30 mg, in divided doses; some patients may require 40–60 mg daily.

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Given that approximately 67% of the administered dose is converted to ritalinic acid in urine, the estimated systemic dose is approximately 15–40 mg. In children, it is recommended that methylphenidate be initiated in small doses with gradual weekly increments.

Methylphenidate is particularly useful in the pediatric population but given the short plasma half-life of this compound (approximately 1–2 h), children have to either remember or be reminded and monitored to adhere to their dosage schedule (Pelham et al., 1990). For adequate absorption, the tablets have to be taken an hour before meals. Orally administered methylphenidate is also subject to hepatic first-pass effect and may be associated with certain unwanted gastrointestinal effects. Thus, there is a rationale for investigating alternate delivery systems for enhanced efficacy, safety and increased patient compliance.

Iontophoresis may be defined as the facilitated movement of ions of soluble salts across a membrane under an externally applied potential difference (Newman, 1991; Singh and Maibach, 1994). An electric current is induced across the skin by a low voltage. The application of a constant current is controlled by an electronic device that adjusts the voltage in response to changes in skin electrical resistance. Charged drugs as well as other ions are carried across the skin as a component of induced ion flow. Iontophoresis has been shown to effectively deliver a large variety of compounds. Factors affecting iontophoretic delivery have been described in various review articles (Banga and Chien, 1988; Srinivasan et al., 1989; Singh and Maibach, 1994). Some important considerations include: flux proportionality to applied current density (current per unit area), ions other than drug will decrease the efficiency of iontophoretic transport of the drug (also known as transport number), and a current of up to 0.5 mA/cm^2 is believed to be suitable for patient tolerance. Since drug delivery is proportional to applied current, a significant advantage of iontophoresis includes the possibility of pre-programming the drug delivery. The drug delivery may be dose-tailored on an individual basis or time-tailored in a constant or pulsatile fashion. The onset of action with iontophoretic treatment is short, typically of the order of minutes, in contrast to hours by passive transdermal delivery.

Chemically, methylphenidate is methyl α-phenyl-2-piperidineacetate (Fig. 1). The free base methylphenidate has a molecular weight of 233 and a pK_a of 8.9. The hydrochloride salt is freely soluble in water and its molecular weight is 270.

The present study was undertaken to make an initial technical feasibility assessment for the transdermal delivery of methylphenidate in its hydrochloride salt form. A systemic daily dose of 15–40 mg was targeted. The approach involved looking into the drug transport by passive (no applied current) and direct current iontophoresis using an in vitro excised human skin model. The effects of drug concentration and applied current density were examined. Free solution mobility of methylphenidate was estimated from conductivity measurements and compared with mobility of methylphenidate estimated from skin flux measurements.

2. Materials and methods

2.1. Chemicals

Methylphenidate hydrochloride and methylphenidate hydrochloride reference standard were obtained from Novartis Corporation (Suffern, NY). Monobasic sodium phosphate, dibasic sodium phosphate, sodium chloride and triethylamine were obtained from Fisher Scientific (Fairlawn, NJ). Gentamicin sulfate was obtained from Sigma Chemical (St Louis, MO), monobasic potassium phosphate, methanol and potassium chloride were obtained from J.T. Baker (Phillipsburg, NJ), and 1.0 N hydrochloric acid and glacial acetic acid were purchased from Mallinck-

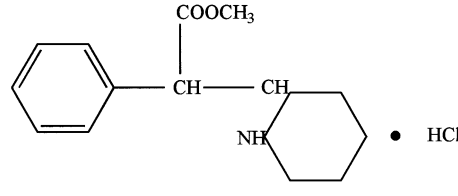

Fig. 1. Chemical structure of methylphenidate hydrochloride.

rodt (Paris, KY). Silver wire (0.5 mm diameter) was obtained form Aldrich Chemical (Milwaukee, WI). Distilled, de-ionized water (Milli-Q Water System, Millipore, Bedford, MA) was used to prepare aqueous solutions.

2.2. Human skin

Dermatomed dorsal human cadaver split-thickness skin (comprised of stratum corneum, epidermis and a portion of dermis) was utilized. The skin had been cascade frozen at the skin bank and stored at −70°C. It was thawed prior to use in 32°C receiver solution (10 mM phosphate buffer containing 0.15 M NaCl) for at least 30 min.

2.3. HPLC assay

Methylphenidate was assayed by reverse-phase high performance liquid chromatography using a model 715 WISP, 610 fluid unit, a 600E system controller and a 486 programmable absorbance detector (Waters, Milford, MA) at a wavelength of 209 nm, and a Waters μ-Bondapak C18 column (0.39×30 cm^2). The mobile phase was a mixture of 0.02 M monobasic potassium phosphate and methanol in the ratio 66:33 (by volume) containing 0.1% triethylamine and the pH adjusted to 4.6 with glacial acetic acid. The retention time of methylphenidate was 9 min at the flow rate of 1.6 ml/min.

2.4. Solubility determination

Saturated aqueous methylphenidate solutions were prepared by equilibrating an excess of methylphenidate hydrochloride in centrifuge tubes for 48 h at 32°C while stirring in temperature-controlled, water-jacketed beakers. The solutions were then centrifuged at 2500 rpm at 32°C for 15 min in an IEC Centra-8R centrifuge. The supernatant was removed and analyzed for methylphenidate content.

2.5. Conductivity measurements

Various concentrations (1.85–370 mM) of methylphenidate were prepared in distilled, deionized water. The solution conductivity was measured using conductivity cell CDC 314 (cell constant = 3.16/cm) and a CDM83 Conductivity meter (Radiometer America, Cleveland, OH). Prior to the measurements, the instrument and the conductivity cell were calibrated using 0.05% NaCl, which had a conductivity of approximately 1 mS/cm. Duplicate determinations of the conductivity were made for each solution.

2.6. In vitro skin permeation

2.6.1. Passive delivery (no current applied)

Horizontal flow-through cells (Crown Glass, Somerville, NJ) were maintained at 32°C using a water circulator (Haake D1, Germany). The skin was mounted on the diffusion cell with the stratum corneum side facing the donor compartment. The receiver solution for permeation studies contained 0.01 M sodium phosphate and 0.15 M sodium chloride (pH 7.4). All buffers were filtered through Corning # 25954-1L filters (0.22 μm, Fisher Scientific). The receiver solution was pumped from the reservoir to the cell using a Rabbit-Plus® peristaltic pump (Rainin Instrument, Woburn, MA.). The receiver solution was degassed for 3 h under house vacuum before use. Fresh Teflon® tubing (80 cm length, 0.1 cm inside diameter) connected the diffusion cell to a Retriever II fraction collector (ISCO, Lincoln, NE.)

2.6.2. Iontophoretic delivery

The split-thickness skin was mounted in side-by-side diffusion cells as described in the passive studies. A Keithley 500A Measurement and Control System was used as a constant current source. The current was applied using silver/silver chloride driver electrodes to prevent electrolysis of water. The potential drop across the skin was determined by another pair of silver/silver chloride reference electrodes placed closer to the skin. The reference electrodes were placed 0.9 cm from either side of the skin, while the driver electrodes were 2.7 cm from the skin surface. The distance separating the driver and reference electrodes in a half cell was 1.8 cm. The driver cathode was electroplated at constant current in a solution of 1 M KCl/1 M HCl (0.3–1 mA for 12–14 h), while

the driver anode and reference electrodes were lightly plated (0.3–1 mA for 30–40 min) using a Keithley model 220 Programmable current source. The electrodes were stored shorted together in 1 M NaCl.

The effects of current density (0.075–0.5 mA/cm^2) and donor methylphenidate concentration (0.03–0.8 M) were examined using skin from a single donor. Since methylphenidate is positively charged, anodal iontophoresis was employed by placing a positively charged anode in the donor compartment and a negatively charged cathode in the receiver compartment. All skin samples were initially screened for integrity by passing a small amount of current (20–25 μA) and measuring the voltage drop across the skin. Both donor and receiver chambers were filled with normal saline for skin resistance measurements. The selected skin samples had specific resistance greater than 10–15 kΩ cm^2.

Based on calculations from Faraday's law, the chloride counterion concentration provided by donor concentrations of methylphenidate was sufficient for the duration of experiment, so no extraneous ions were added on the donor side. In the current density study, the skin was mounted in the diffusion cells and, after charging the donor compartment with aqueous methylphenidate hydrochloride solution, a passive segment (in the absence of current) was run overnight (10–12 h). The current was then switched on for 9–10 h for each successive active (iontophoretic) segment. The effect of donor solution concentration was evaluated in a separate study at a constant current density of 0.2 mA/cm^2. These experiments were conducted with a new donor concentration applied at the beginning of each successive segment. On a few occasions between the successive active segments, samples were collected in the absence of current to assess the reversibility of the skin exposed to electric current. Fresh driver cathodes were used during each active segment in both series of experiments.

2.7. Sample collection and data analysis

The receiver effluent was automatically collected into tared test tubes and the flow rate of the receiver solution was determined by weighing the test tubes containing samples on a Mettler AE 240 Electronic Balance (Mettler Instrument, Hightstown, NJ.). Methylphenidate flux values were calculated by linear regression of the steady-state region and expressed as the amount delivered per unit diffusional area per unit time (μg/(cm^2 h)). The lag time was calculated by extrapolating the steady-state flux to the x axis and then correcting for the 'dead volume' of the flow-through cell's receiver solution divided by the flow rate through the receiver (Sclafani et al., 1993). All the data were calculated in terms of the free form of methylphenidate.

3. Results and discussion

3.1. Solubility

The solubility of methylphenidate hydrochloride in unbuffered aqueous solution at 32°C was found to be 191 ± 6 mg/ml (methylphenidate concentration) with a resulting solution pH of 3.0, at which methylphenidate was all protonated.

3.2. Passive transport

The passive flux of protonated methylphenidate from near-saturated methylphenidate hydrochloride solutions was observed to be 12.3 ± 2.6 μg/(cm^2 h) ($n = 3$). A lag time of approximately 5 h was estimated for the passive transport of protonated methylphenidate. Based on this data, the patch size required for delivering a daily systemic dose of 15–40 mg will be fairly large (transport area, 70–185 cm^2).

3.3. Iontophoretic transport

3.3.1. Effect of current density

Fig. 2. shows the flux of methylphenidate as a function of time for various current densities. The 'on' portion signifies when the current was turned on and 'off' signifies when the current was switched off. As can be seen, iontophoresis significantly facilitates the transport of protonated methylphenidate relative to passive transport. The

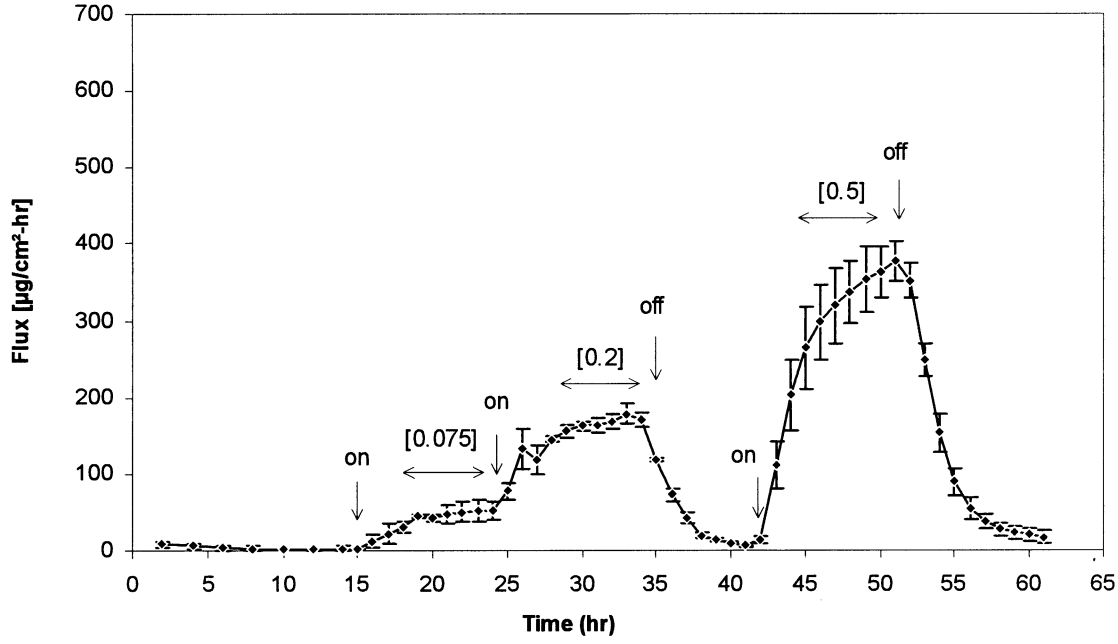

Fig. 2. Methylphenidate flux as a function of time at different current densities and an applied methylphenidate concentration of 0.5 M, pH 3.5 ($n=4$). […],current density in mA/cm^2.

flux values of methylphenidate across skin exposed to 0.2 mA/cm^2 for 10 h declined rapidly soon after switching off the current, while the flux values across skin exposed to 0.5 mA/cm^2 were relatively higher as compared with passive flux 10 h after switching off the current. This indicates that the iontophoresis procedure is reversible, especially at low current densities. Relatively higher passive fluxes across iontophoresis-treated skin, as compared with passive fluxes, may be either due to increased passive permeability of skin exposed to electric current or the emptying of the skin depot formed during iontophoretic episode. These results suggest that methylphenidate iontophoretic delivery is feasible and can be preprogrammed by switching the current on or off, and higher doses may be delivered by increasing the current density. This regimen may be particularly useful for compounds such as methylphenidate, which require dose adjustments on an individual basis.

Fig. 3. shows a flux–current density plot. The flux was found to be fairly linear over the current density range studied, with a slope (also termed iontophoretic efficiency) of 700 µg/(mA h). It follows that, in order to achieve a daily systemic dose of 15–40 mg methylphenidate at an applied current density of 0.5 mA/cm^2, a minimum transport area of 2–5 cm^2 for 24 h application or 4–10 cm^2 for 12 h application will be required.

3.3.2. Effect of drug concentration

As shown in Fig. 4, the steady-state flux of methylphenidate increases with concentration up to 0.1 M. At higher drug concentrations, there is little change in drug flux with increasing drug concentration, probably due to charge saturation of the aqueous conducting pathways of the skin.

3.4. Mobility estimations of methylphenidate from conductivity and skin flux measurements

The migration flux of protonated methylphenidate () across the skin may be given by:

$$J_m^{migr} = \frac{t_m}{z_m F} I \quad (1)$$

where z_m is the charge on methylphenidate ($+1$), F is Faraday's constant and is equal to 96 500

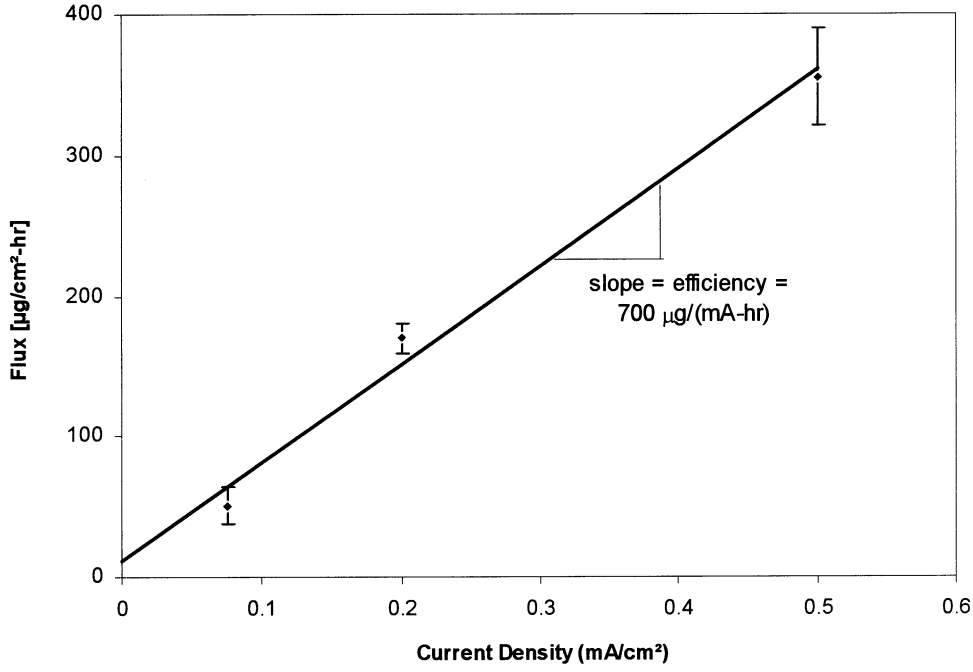

Fig. 3. Relationship between methylphenidate skin flux and applied current density at a methylphenidate concentration of 0.5 M (pH = 3.5, $n = 4$).

C/equiv., I is the current density expressed in A/cm^2 and t_m is the transport number of methylphenidate. In iontophoresis, every ion in the formulation and endogenous ions in the skin will carry a fraction of applied current. The number of interest is the transport number of the active ingredient (methylphenidate in this case, t_m), which may be defined as the fraction of total current carried by the drug:

$$t_m = \frac{z_m^2 u_m c_m}{\sum_i z_i^2 u_i c_i} \quad (2)$$

where i represents all ions in the system, and z, u and c represent charge, mobility and concentration of a given ion, respectively. Eq. (2) indicates that the transport number of an ion is related to its mobility and to the mobility of other competitive ions. The mobility of the ions depends on their size, and charge density, as well as the degree of hydration. The faster the competitive ions move, the less the fraction of current carried by the methylphenidate, resulting in lower methylphenidate flux. In addition, the concentration of competitive ions in both donor and receptor solutions also affects the transport number of methylphenidate. Eqs. (1) and (2) suggest that it may be possible to estimate the drug transference number and iontophoretic flux if the skin mobility of the drug and competing ions is known. It is experimentally difficult to determine the skin mobility of a drug. Free solution mobility of a drug may, however, be estimated from solution conductivity measurements. Methylphenidate free solution mobility was assessed from conductivity measurements as follows.

According to Kohlrausch's law, at low concentrations, the equivalent conductance (Λ) decreases with increasing concentration according to:

$$\Lambda_c = \Lambda^o - k_c c^{1/2} \quad (3)$$

where Λ_c is the equivalent conductance at any concentration ($= \Lambda_+ + \Lambda_-$), Λ° is the equivalent conductance at infinite dilution

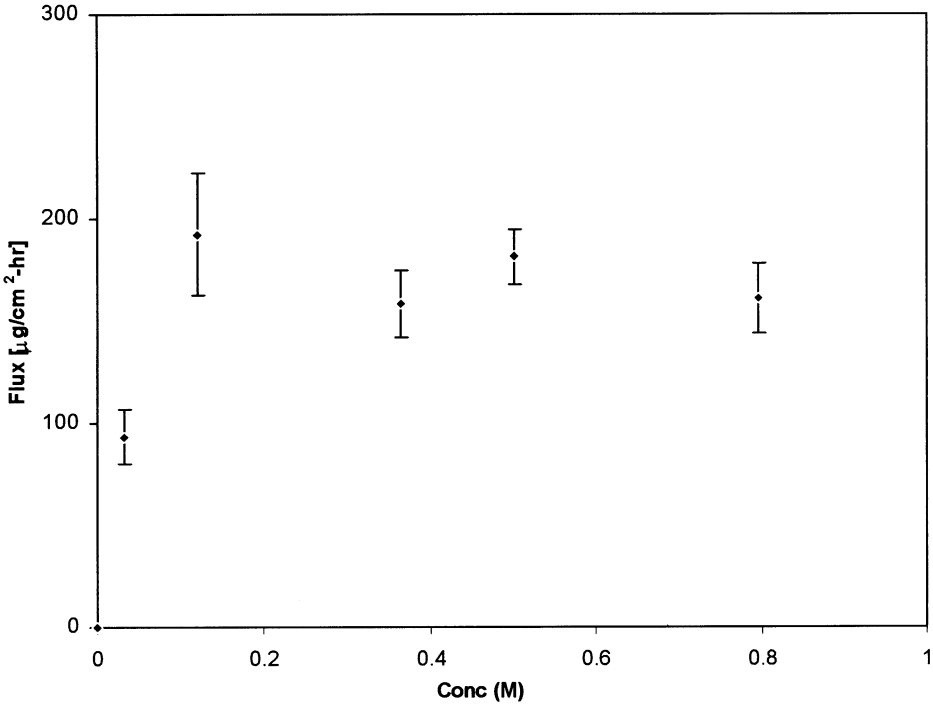

Fig. 4. Relationship between applied concentration and iontophoretic skin flux of methylphenidate at an applied current density of 0.2 mA/cm^2 ($n = 4$).

($= \Lambda^\circ_+ + \Lambda^\circ_-$), and k_c is an experimental constant. When equivalent conductance (Λ) and square root of methylphenidate concentration were plotted (Fig. 5), the limiting slope k_c was achieved only at methylphenidate concentration less than 20 mM. Extrapolation of the data in this region to zero concentration gave $\Lambda^\circ = 140$ cm^2 S/mole. Subtracting the value of Λ° (Cl^-) = 76.31 cm^2 S/mole gives Λ° (protonated methylphenidate) = 63.69 cm^2 S/mole.

Mobility of chloride is $u_{Cl} = \Lambda^\circ_{Cl}/F = 76.31/96\,500 = 7.9 \times 10^{-4}$ cm^2/(V s), and. mobility of protonated methylphenidate is $u_M = \Lambda^\circ_M/F = 63.69/96\,500 = 6.6 \times 10^{-4}$ cm^2/(V s).

From the skin flux measurements, methylphenidate mobility of 2.0×10^{-4} cm^2/(V s) was estimated using Eqs. (1) and (2), which compares reasonably with the free solution mobility of 6.6×10^{-4} cm^2/(V s). This may suggest that free solution mobility of a drug (of relatively small size) is comparable with its mobility in the skin and may be used as a first approximation to assess the iontophoretic flux of a drug under given conditions.

Iontophoresis significantly enhanced transdermal delivery of methylphenidate, as compared with passive transport. The in vitro results suggest that a methylphenidate daily systemic dose of 15–40 mg can easily be achieved by iontophoresis with rapid onset of action. Free solution mobility of a drug may be used for preliminary assessment of its iontophoretic flux. This approach, however, needs to be tested for other compounds with different physicochemical properties, particularly for macromolecules. In vivo studies will be required to support in vitro conclusions and develop in vitro–in vivo correlations.

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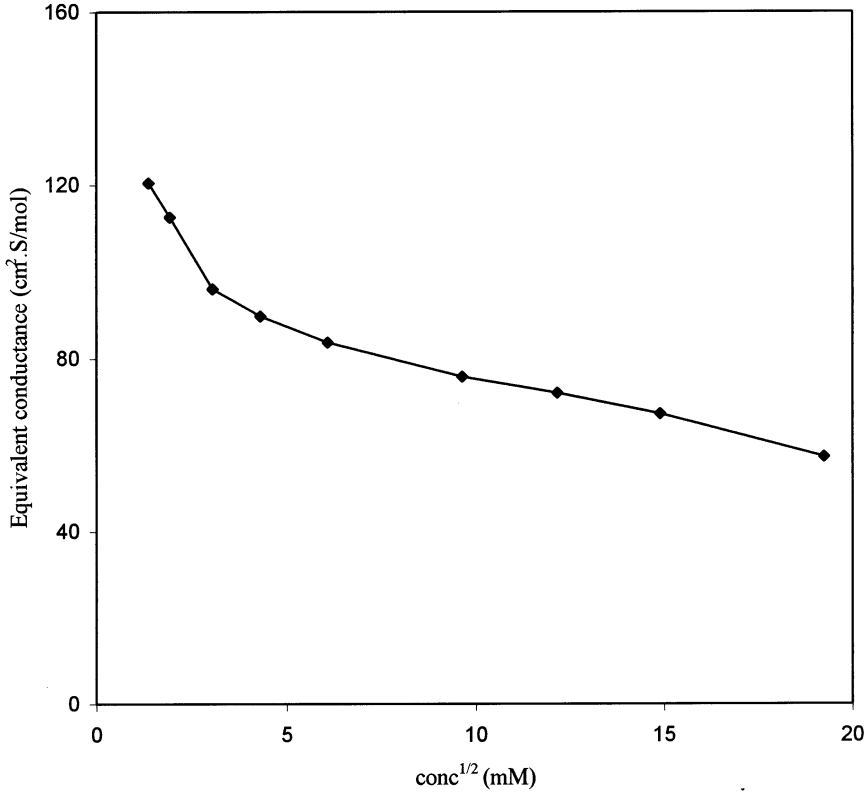

Fig. 5. Relationship between equivalent conductance and square root of methylphenidate concentration at 32°C.

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