

FEASIBILITY OF ROSIGLITAZONE MALEATE FOR TRANSDERMAL DELIVERY.

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ABSTRACT

Delivering medicine to the general circulation through the skin is associated with greater advantages compared to that by the oral route and hence the purpose of this investigation was to study the potential of rosiglitazone maleate for transdermal delivery using passive diffusion and iontophoresis. Physicochemical parameters of rosiglitazone maleate like solubility, pKa, octanol/vehicle and skin/vehicle partition coefficient were determined. Solubility study was carried out in binary vehicle of ethanol-water. Rosiglitazone maleate was delivered from hydro-alcoholic vehicle of different composition and in vitro skin permeability through full thickness ear skin of domestic pigs (*Sus domesticus*) was observed in a Franz-diffusion cell using 0.9% NaCl as the receptor fluid. For iontophoretic diffusion, a current density of 0.5mA/cm² was used. Permeation rate of rosiglitazone maleate had increased with increase in donor drug concentration (P<0.01) up to the level of 213.71 µmol/ml in both passive diffusion and iontophoresis, but thereafter increase in steady state flux was not statistically significant indicating the donor concentration of 213.71 µmol/ml was optimum. Highest steady state flux (0.571 ± 0.031µmol/cm²hr) was recorded in iontophoresis, which was approximately 7 times higher than the target flux calculated on the basis of minimum effective concentration. As the target flux of rosiglitazone maleate is moderate (1.09 µmol/hr) and good skin permeability was observed in the study, it appears that rosiglitazone maleate is a promising candidate for transdermal delivery.

Key words: Diabetes, Franz diffusion cell, Passive diffusion, Iontophoresis, Pigskin

INTRODUCTION

Diabetes mellitus (DM) is one of the fastest growing diseases worldwide and it imposes serious constraints over the lifestyle of individuals because of its chronic complications. It is a lifelong disease marked by high levels of sugar in blood. Poorly controlled diabetes leads to damage of end organs such as kidneys, heart, brain and eyes, which not only affects the quality of life but also increases the health expenditure to the individual and at large to the society¹. Diabetes may be categorized into several types, but the two major types are type-1 or insulin dependent diabetes mellitus (IDDM) and type-2 or non- insulin dependent diabetes mellitus (NIDDM). Type-2 or NIDDM is caused by anomalies in gluco-receptor of β-cells and is often associated with the down regulation of insulin and 98% of all diabetes cases amongst middle aged people suffer from this syndrome.²⁻³ Type-2 diabetes is a

common fast growing disease that affects about 5% of the population worldwide. The disease is complicated by specific cardiovascular events, and the mortality rate is 2–3 times higher than in the background population⁴. Rosiglitazone maleate, belonging to the class of thiazolidinedione, is an oral anti-diabetic drug, which is particularly suitable for diabetic patients who are overweight and for whom metformin is contraindicated.⁵⁻⁶ It improves the glycemic control primarily by increasing peripheral insulin resistance and sensitizing the skeletal muscle, liver and adipose tissue to the actions of insulin, in addition to improving beta-cell function⁷. However its oral dosage forms are associated with some unwanted effects like hypoglycaemia, headache, weight gain, anemia, dizziness, pruritus and gastric disturbance like nausea, vomiting and anorexia. The major side effects of rosiglitazone include peripheral and pulmonary oedema, decreased visual acuity and liver dysfunction⁸. Following oral administration, rosiglitazone is rapidly absorbed (t_{max} 1-2 hr) and is primarily metabolized in the liver by cytochrome P450

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group of enzymes⁹. With an elimination half-life of 3 to 5 hr¹⁰ the drug needs frequent administration. A recent study reported that exposure to high-therapeutic concentrations of rosiglitazone can cause fourfold increase in pulmonary endothelial permeability, which could be clinically relevant especially at higher doses and at times of peak plasma drug concentration¹¹. These and a high risk of heart failure have resulted in a ban over its use in several countries including India. As transdermal delivery can bypass the first pass metabolism and deliver the drugs in rate-controlled manner, it is desirable for anti-diabetic therapies and a number of anti-diabetic agents have been screened for transdermal development.¹²⁻¹³ Recently, a study has indicated that sustained delivery of rosiglitazone through transdermal route can help avoid the toxicity due to sudden high blood concentration. This study was taken up to screen the potential of rosiglitazone maleate for transdermal delivery.

MATERIALS AND METHODS

Materials

Rosiglitazone maleate was obtained as a gift sample from Torrent Research Center, Ahmedabad. Passive permeation studies were carried out using Franz diffusion cell, purchased from Neutron Scientific, Kolkata. Iontophoretic direct current source (model no. PSU 2510/Lab, digital display, current 0-10 mA, voltage 0-25 V) was purchased from C-Tech Mumbai, India. Iontophoretic diffusion cell was fabricated by Navin Scientific Glass Products, Bangalore. Silver-silver chloride electrode was prepared as per the standard procedure.¹⁴ Silver rods (99.98% pure, 0.5 mm thickness) were used as connecting wires. Ethanol, sodium chloride, sodium acetate, octanol and acetic acid were obtained from S.D. Fine-Chem., Mumbai, India. All the reagents/chemicals used were of analytical grade. Experiments were conducted with ultra pure water (resistivity 18.2 MΩ cm) obtained from Milli-Q academic system (Millipore Pvt. Ltd., Bangalore, India).

Methods

Quantification of the drug

Rosiglitazone maleate was quantified by HPLC. Hitachi high performance chromatograph with a reversed phase Kromasil 300-4, C-18, 5 μm column (250 X 4 mm internal diameter) equipped with Hitachi L-7110 pump, L-7400 UV detector and Winchrome-99 software was used. For making standard graph, working standards were prepared in 0.9% NaCl (5-50 μg/ml) and injected

into the column (20 μl). The column was eluted with the mobile phase consisting of acetate buffer (80 mM) and acetonitrile (55:45 v/v, pH 4.37) and the detection was carried out at 316 nm. The mobile phase was delivered at a flow rate of 1 ml/min and the retention time recorded was 4.09 min. The plot of peak area versus respective concentration of rosiglitazone maleate was found to be linear ($Y= 173226X$) with the correlation coefficient (R) of 0.991.

Solubility determination

Excess amounts of the drug was taken into glass vials and dissolved in different solvent systems (water, 0.9% NaCl, water-ethanol systems of various proportions) to get saturated solutions. The solutions were kept at rest for 24 hr to assist the attainment of equilibrium with the un-dissolved drug particles. The supernatants were decanted and filtered through Whatman filter no.42¹⁵. The filtrates were suitably diluted to measure the concentrations by HPLC.

Partition coefficient

Octanol and water were mutually saturated by shaking in a separating funnel, allowed to stand for 24 hr and separated. Standard solution of the drug was prepared in this octanol saturated water. Octanol (10 ml) was added to equal volume of this standard drug solution in a separating funnel and was kept for 24 hr at room temperature with intermittent shaking. Finally, the water layer was separated, clarified by centrifugation and assayed for drug content.

pKa determination

pKa was determined as suggested by Silcocks¹⁶. It was determined by using a Digisun DI -707 pH meter equipped with a glass electrode and a silver-silver chloride reference system. Solutions were made at different concentration levels and pH was noted from which pKa was determined by using equation (1):

$$H^+ = \sqrt{Ka \cdot C} \quad (1)$$

Where H^+ is hydrogen ion concentration, C is the molar concentration of dissociating moiety and Ka is the dissociation constant.

Preparation of skin membrane

From a local abattoir, ears were obtained from freshly slaughtered pigs (*Sus domesticus*). After removing the thick layer of fat from the dermal side, the skin surface was cleaned of the residual fat using isopropyl alcohol soaked in cotton¹⁷. The average thickness was found to be 0.95 mm. Finally the skin was washed with water

Table 1. Physicochemical parameters* of rosiglitazone maleate

Solubility in 0.9% NaCl ($\mu\text{mol/ml}$)	Solubility in Water ($\mu\text{mol/ml}$)	Partition Coefficient Octanol/Water	pKa
1.24 \pm 0.04	1.25 \pm 0.03	1.38 \pm 0.01	7.97 \pm 0.68

*Each value is the mean \pm SE (n= 3).

and stored at refrigerator in aluminum foil packing and was used within 48 hr¹⁸.

Procedure of passive permeation

The excised skin was mounted between the two half-cells of Franz diffusion cell with the dermal side in contact with receptor fluid (0.9% NaCl) and was equilibrated for 1 hr. The area available for diffusion was about 1 cm² and the volume of the receiver fluid was 25 ml. The donor cell was covered with an aluminium foil to prevent the evaporation of vehicle. The fluid in the receptor compartment was maintained at 37 \pm 0.5^o C. Rosiglitazone maleate in water (1.24x10⁻⁶ mol/ml) was placed in the donor compartment. The entire assembly was kept on a magnetic stirrer and to maintain the sink condition, 5 ml of solution was withdrawn from receptor compartment at hourly interval for a period of 8 hr and assayed for drug content¹⁹.

Procedure of iontophoretic diffusion

For iontophoresis diffusion cell was modified as suggested by Glikfield et al²⁰. The apparatus essentially consists of a glass molded large receiving chamber provided with two parallel ports on the topside and a sampling port on the side. Two upper chambers are made from open-ended cylindrical glass tubes, the outer diameters of which are equivalent to the inner diameter of the parallel ports. The lower 10 mm of these tubes are slightly constricted to allow a clearance of approximately 2mm on the side. This ensures easy fitting. After the skin is tied at this constricted end, the effective diameter increases and becomes exactly equal to inner diameter of extended ports. Once slipped into parallel ports they stay attached by glass joints forming two separate chambers with skin at the base. Both the skins touch the receptor solution at the same depth and each chamber houses one electrode. Once the battery is switched on current flows through the skin placed in

anodal compartment into receiving solution below and reaches the cathodal electrode through the skin tied to cathodal end. Donor solution (2 ml) was filled in the cathodal chamber while the anodal chamber housed the return electrode. For our study, silver/silver chloride electrode was inserted into the donor compartment whereas silver plate was inserted into anodal chamber as return electrode. Direct current (0.5 mA cm⁻²) was used throughout experiment. The receptor fluid (5 ml) was withdrawn at regular intervals and replaced with 0.9% NaCl to maintain sink condition. The samples were assayed by HPLC²¹.

Data analysis

The cumulative amount permeated (CAP) per cm² was plotted against time and the slope of the linear portion of the plot was taken to be the steady state flux. Permeability coefficient and diffusion coefficient were calculated using the following formulas:

$$K_p = \frac{J_{ss}}{C_d} \quad (2)$$

$$D = \frac{K_p \cdot h}{K} \quad (3)$$

Where K_p represents permeability coefficient, J_{ss} , steady-state flux, C_d , concentration of drug in donor compartment, D , diffusion coefficient, K , skin/vehicle partition coefficient and h the thickness of skin.

Statistical analysis

Data analysis was done by one-way ANOVA followed with Bonferroni's test by using the software GraphPad InStat version 3.0.

RESULTS AND DISCUSSION

As inadequate permeation is a major limiting factor for development of transdermal delivery system, the drugs with high effective concentration and clearance are difficult candidates for transdermal delivery. However, rosiglitazone maleate, a potent molecule with a low total clearance (0.68 \pm 0.16 ml/min/kg) appears to be a good candidate²². Transdermal permeation is a composite parameter influenced by a number of physicochemical and biological factors. In addition to molecular weight, partition co-efficient and solubility, the pKa of a drug, which determine its extent of ionization, is of prime importance²¹. Rosiglitazone maleate suffers from low aqueous solubility, but has a favorable partition coefficient of 1.38 (Table 1). The experimentally determined pKa of

Table 2. Solubility study of rosiglitazone maleate in water- ethanol binary systems

Sl. No	System Water:Ethanol	Mean Solubility* (mg/ml)	SD Solubility* (mg/ml)	Mean Solubility* (mol/ml)	SD Solubility* (mol/ml)	RSD ^a
1	100:0	0.59	0.03	1.24x10 ⁻⁰⁶	6.33 x10 ⁻⁰⁸	5.08
2	90:10	10.85	1.48	2.29 x10 ⁻⁰⁵	3.12 x10 ⁻⁰⁶	13.64
3	80:20	36.04	1.43	7.61 x10 ⁻⁰⁵	3.02 x10 ⁻⁰⁶	3.96
4	70:30	54.88	3.38	0.000115	7.13 x10 ⁻⁰⁶	6.15
5	60:40	77.5	2.98	0.000163	6.29 x10 ⁻⁰⁶	3.84
6	50:50	101.19	3.5	0.000213	7.39 x10 ⁻⁰⁶	3.45
7	40:60	121.01	2.86	0.000255	6.0 x10 ⁻⁰⁶	2.36
8	30:70	166.69	2.86	0.000352	6.04 x10 ⁻⁰⁶	1.71
9	20:80	121.86	3.47	0.000257	7.32 x10 ⁻⁰⁶	2.84
10	10:90	89.35	2.55	0.000188	5.38 x10 ⁻⁰⁶	2.85
11	0:100	41.75	2.59	8.81 x10 ⁻⁰⁵	5.46 x10 ⁻⁰⁶	6.20

*Each value is the mean \pm SD (n= 3). ^aRSD- Relative Standard Deviation.

the rosiglitazone was found to be 7.9, which indicates the drug is fractionally ionized in aqueous media. Concentration of the actives in the delivery system is the most crucial factor that affects skin permeability. As rosiglitazone maleate has poor water solubility, to increase the donor concentration, a co-solvent was necessary. It is evident in Table 2 that the solubility had increased up to a certain point with the increase in ethanol percentage, but thereafter, the solubility had declined. The highest solubility in hydro-alcoholic system was found to be 166.69 \pm 2.86 mg/ml, when the alcohol content was 70%.

The values of the octanol/vehicle and skin/vehicle partition coefficients for rosiglitazone maleate are depicted in Table 3 which shows with the increase of ethanol content, partition co-efficient of rosiglitazone maleate had decreased (P< 0.01). This might be due to the increased affinity of the drug for the vehicle, resulting in its lesser partitioning into the lipophilic phase. Similar phenomena were observed in glipizide and fluoxetine also²³. The finding suggests that though

Table 3. Comparative lipophilicity of rosiglitazone maleate at different donor systems.

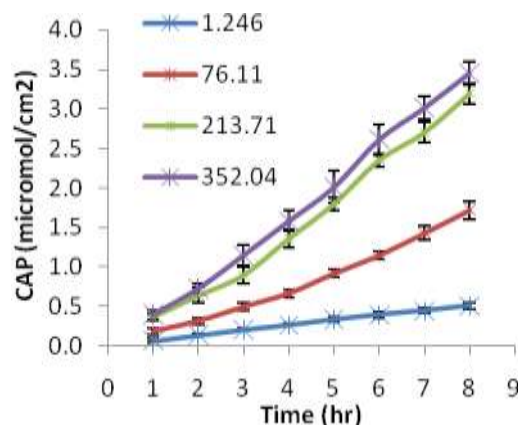
Donor System Vehicle	Partition coefficients* Skin/Vehicle	Partition coefficients* Octanol/Vehicle
0% Ethanol	1.134 \pm 0.281	1.380 \pm 0.151
20% Ethanol	0.367 \pm 0.145**	0.321 \pm 0.086**
50% Ethanol	0.114 \pm 0.014**	0.216 \pm 0.164**
70% Ethanol	0.034 \pm 0.012**	0.134 \pm 0.067**

*Each value is the mean \pm SE (n= 3).

** indicates values are significantly lower than that obtained from the aqueous vehicle (0% ethanol) P<0.01.

ethanol increases the donor concentration by increasing solubility, very high level of ethanol might even oppose the permeation of the drug through the skin.

Figure 1 shows the passive permeation of rosiglitazone through porcine skin at different donor concentrations. Pigskin was known to be a good animal model for the human skin as the permeation rate of tritiated water through dermatomed, full thickness pigskin is found to be very slightly greater than that through the human tissue. A statistically significant correlation has been reported between the values obtained by *in vitro* permeation through pigskin and that of human skin *in vivo*²⁴ Although the stratum corneum of the pig is

**Figure 1. Passive permeation of rosiglitazone maleate at different donor concentrations.**

Each point represents the mean \pm SE (n=3). CAP indicates cumulative amount permeated.

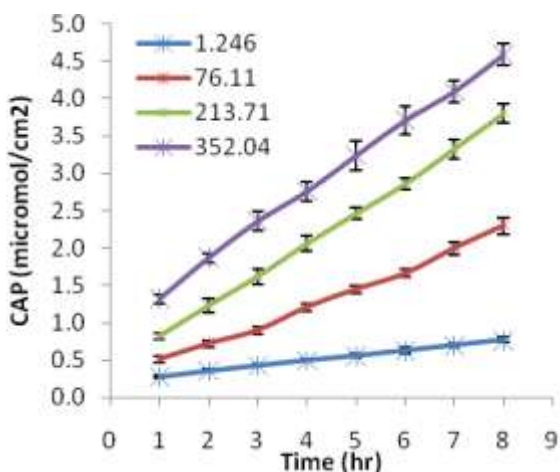


Figure 2. Iontophoretic permeation of rosiglitazone maleate at different donor concentrations.

Each point represents the mean \pm SE (n=3).

almost twice as thick as the human skin, it is very similar to human tissue in the density of hair follicles; both contain approximately 11 follicles per cm^2 . However, pigskin follicles have coarse hair shafts, with almost twice the diameter of their human counterparts and it is impossible to separate the epidermis from the skin samples by the methods of heat, trypsin or ammonia. Hence the full thickness skin has been used for the experiments²⁵.

Rosiglitazone maleate was delivered as a suspension (infinite dose) at four different donor concentrations (01.246, 76.11, 213.71 and 352.04 $\mu\text{mol/ml}$). For drugs of low solubility, this is particularly necessary as the amount required for prolonged permeation is likely to be higher than the limits of solubility. In suspension, the loss of drug due to permeation is supplemented by the presence of solid drug in the reservoir and the thermodynamic activity is maintained constant.

Addition of ethanol in donor vehicle is considered to be beneficial for two reasons. Apart from increasing solubility, ethanol also possesses a permeation enhancing effect. Ethanol, used as a co-solvent, had been reported to increase the permeation of a wide range of drugs like ibuprofen, flurbiprofen, indomethacin, isosorbide dinitrate, cyclobarbitol, zalcitabine, didanosine and zidovudine²³. However, when the fractions of ethanol exceed 80% v/v, the outer layers of stratum corneum get substantially dehydrated and this can increase the resistance to permeation of both ethanol and drug²⁶. Hence, for the present study, the upper limit of the ethanol concentration in the donor system was confined to

70%. The decision was further justified as above the level of 70%, the solubility of the drug also declined.

In case of passive diffusion, permeation rate of the drug was minimal in the initial hours but increased in the later hours. Increase in permeation rate with the increase in donor drug concentration was statistically significant ($P < 0.01$) up to the level of 213.71 $\mu\text{mol/ml}$, but thereafter the increase was not significant and hence the donor concentration of 213.71 $\mu\text{mol/ml}$ was considered to be optimum. Increase of drug concentration from 213.71 $\mu\text{mol/ml}$ to 352.04 $\mu\text{mol/ml}$ caused minimal benefit in terms of cumulative permeation ($P > 0.05$). At all concentration levels, permeation profiles were found to be linear indicating that the permeation kinetics was more or less zero order ($R^2 = 0.9939$ to 0.9993).

Figure 2 shows the iontophoretic permeation profiles of rosiglitazone maleate delivered at different donor concentrations. A close observation reveals that first hour permeation was high but the rate declined in the later phase. In contrast, the permeation rate was more or less constant in passive process (Figure 3).

Rosiglitazone maleate is ionized at pH 7 and for an ionic species, iontophoresis is thought to be a better option than passive diffusion²⁷. Iontophoretic flux get the added contribution of ionic repulsion and the overall flux is expected to be higher than that of passive diffusion. As expected, overall iontophoretic cumulative amount permeation (CAP) was higher than the passive CAP. Comparatively low first hour flux in passive diffusion can be well explained from the fact, that in the initial hours, there was considerable resistance to permeation as a lag time was associated with the penetration process. The reverse trend in iontophoresis suggests the presence of factors, which helped to overcome the initial opposition. The electrostatic repulsion of iontophoresis is the force responsible for this. However, unlike passive diffusion, permeation rate had declined in the later hours in iontophoresis. A likely explanation is the competition from chloride ions, which had a flux lowering effect. The isoelectric point of the skin varies between 3-4 and at physiological pH, the volume flow is directed towards the cathode. At pH 7, only passive and electro-repulsive fluxes were likely to contribute to the overall permeation. Moreover, electro-osmotic flow may oppose the permeation from the cathodal compartment²⁸. However, electro-osmotic contribution (even if negative) should be more or less same for a given voltage and oppose the flow of drug uniformly. Hence, the decreased iontophoretic flux in

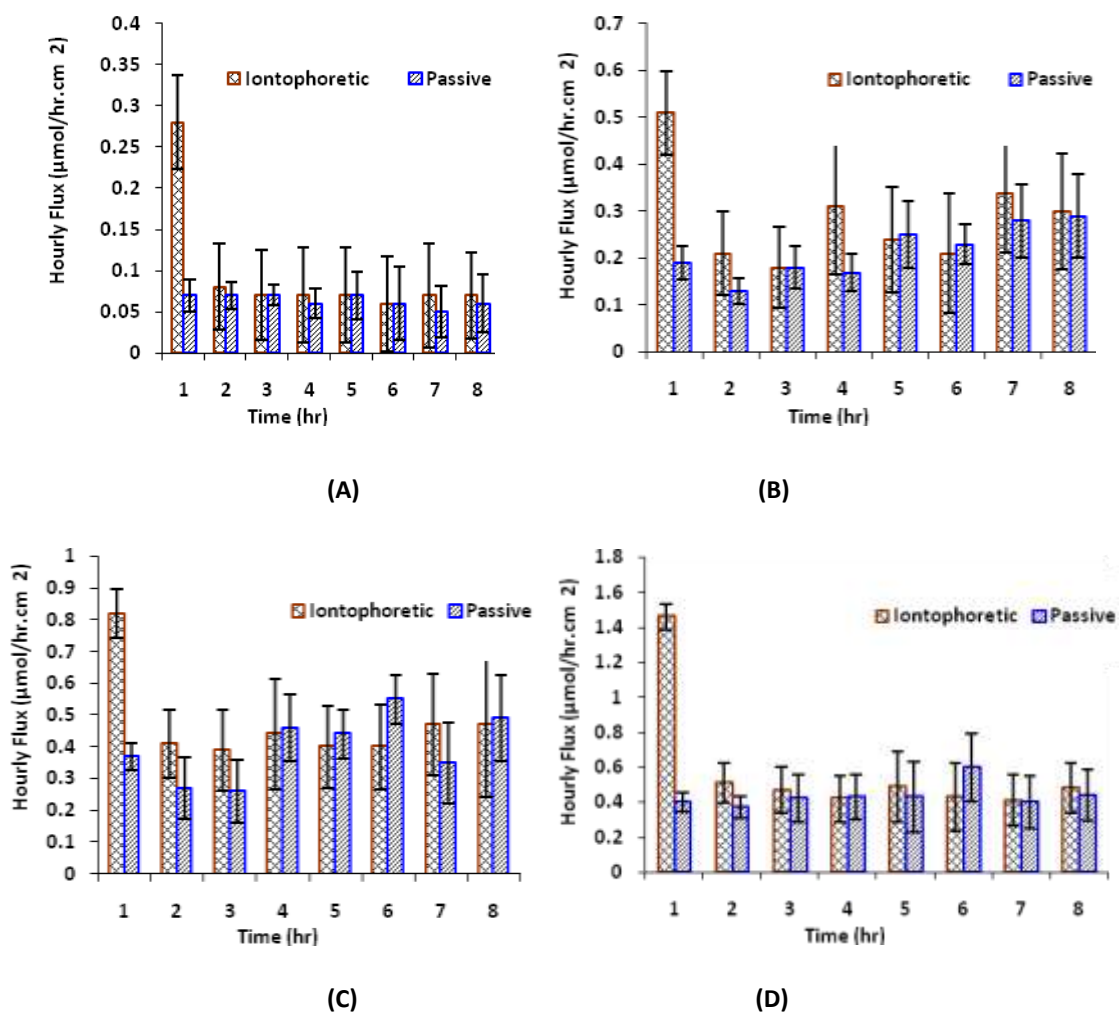


Figure 3. Comparison of hourly flux of rosiglitazone maleate through passive and iontophoretic permeation at different donor concentrations.

Each value represented the Mean \pm SE (n=3). Where A, B, C and D represents the passive and iontophoretic hourly fluxes of rosiglitazone maleate at different donor drug concentrations 0.1, 0.246, 1.1, 213.71 and 352.04 $\mu\text{mol/ml}$, respectively.

the later hours can only be due to the gradually declining electro-repulsive contribution. During the passage of current, the cathodal electrode (Ag/AgCl) receives a steady flow of electron, which results in the liberation of negatively charged chloride ions. As time progressed, the concentration of this chloride ion was likely to increase in the cathodal compartment, which served as the drug reservoir. Since the drug itself was negatively charged, the competition from the chloride ions increased as time progressed, which might have resulted in progressively lesser electro-repulsive contribution²¹.

Table 4 depicts the permeability parameters of rosiglitazone maleate obtained from passive and iontophoretic permeation studies. As expected the highest value was recorded for the lowest donor drug

load. Table 5 compares passive and iontophoretic steady state fluxes (SSF) and enhancement ratios obtained at different donor drug load. Though permeability coefficient is the parameter usually used for comparison purpose, SSF is considered to be the most therapeutically relevant parameter. To assess whether a therapeutic moiety has the potential to be developed into a transdermal system, a target value of SSF (target flux) is assigned for each drug. Target flux (T_f) is the quantity of the drug, which must be delivered to the systemic circulation to elicit a therapeutic response. This quantity is usually fixed on the basis of minimum therapeutic concentration of the drug. For rosiglitazone maleate, this parameter was not reported. Hence, it was calculated indirectly from a single dose (8 mg, tablet) pharmacokinetic data

Table 4. Permeability parameters of rosiglitazone maleate

Donor Concentration ($\mu\text{mol/ml}$)	Passive Permeability Coefficient* ($\text{cm/hr} \times 10^2$)	Iontophoretic Permeability Coefficient* ($\text{cm/hr} \times 10^2$)	Diffusion coefficient* ($\text{cm}^2/\text{s} \times 10^2$)	Diffusion coefficient* ($\text{cm}^2/\text{s} \times 10^2$)
01.246	5.12 \pm 0.0002	7.10 \pm 0.0010	0.43 \pm 0.0009	0.59 \pm 0.0015
76.11	0.29 \pm 0.0002	0.38 \pm 0.0003	0.08 \pm 0.0014	0.10 \pm 0.0008
213.71	0.19 \pm 0.0001	0.26 \pm 0.0002**	0.16 \pm 0.0021	0.22 \pm 0.0018**
352.04	0.12 \pm 0.0001	0.15 \pm 0.0001**	0.34 \pm 0.0005	0.42 \pm 0.0012**

*Each value is the mean \pm SE (n= 3).

** indicates values (of iontophoretic parameters) are significantly higher than the corresponding passive values $P < 0.05$.

Table 5. Comparison of Steady state fluxes and enhancement ratios at different donor drug load

Donor Concentration ($\mu\text{mol/ml}$)	Passive Steady State flux ($\mu\text{mol/hr.cm}^2$)	Iontophoretic Steady State flux ($\mu\text{mol/hr.cm}^2$)	Benefit by Iontophoresis ($\mu\text{mol/hr.cm}^2$)	Enhancement Ratio (R)
01.25	0.059 \pm 0.035	0.101 \pm 0.057	0.04	1.690
76.11	0.220 \pm 0.020	0.288 \pm 0.026	0.068	1.309
213.71	0.408 \pm 0.013	0.481 \pm 0.048	0.073**	1.179
352.04	0.434 \pm 0.017	0.571 \pm 0.031	0.140**	1.32

*Each value is the mean \pm SE (n= 3).

** indicates the benefit of iontophoresis is statistically significant. $P < 0.05$.

reported by Cox et al.²⁹ by using the principle of superposition. In superposition, concentration of drug in blood or plasma after multiple dosing can be predicted from the concentration obtained in a single dose study, provided that the drug follows linear pharmacokinetics³⁰.

The pharmacokinetic study conducted by Cox et al. had shown that the drug undergoes monoexponential decay or linear kinetics. Hence, the principle of superposition could be applied for this drug. Assuming the clearance value of 0.68 ± 0.16 ml/min/kg¹⁹ and dosing interval of 24 hr, the steady state plasma concentration calculated for C_{ss} minimum, C_{ss} average and C_{ss} maximum were found to be 12.2ng/ml, 159 ng/ml and 613 ng/ml. According to these values, the target fluxes were 29.86 $\mu\text{g/hr}$ (0.083 $\mu\text{mol/hr}$) for C_{ss} minimum and 389.23 $\mu\text{g/hr}$ (1.09 $\mu\text{mol/hr}$) for C_{ss} average respectively.

In this study, the highest SSF obtained was 0.571 ± 0.031 $\mu\text{mol/cm}^2/\text{hr}$. This value is approximately 7 times higher than that of the therapeutic requirement if the desired plasma concentration is taken as 12.2 ng/ml (C_{ss} minimum) and an application

area of 2 cm^2 seems to be sufficient to supply the need, if the target is set at the higher value (1.09 $\mu\text{mol/hr}$). Recently, a study has indicated that sustained delivery of rosiglitazone through transdermal route can help avoid the toxicity due to sudden high blood concentration³¹. Albeit further studies in human skin and live animals are required to substantiate the permeation potential of rosiglitazone maleate, the findings of this study clearly suggest that the drug is a promising candidate for transdermal delivery.

CONCLUSION

In both passive diffusion and iontophoresis, rosiglitazone maleate had shown good skin permeability. However, as enhancement of steady state flux was minimal in the later hours of iontophoresis, the drug appears to be a promising candidate for passive transdermal delivery.

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