

Iontophoretic Transdermal Delivery of Methotrexate

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ABSTRACT: The aim of this work was to study the factors affecting transdermal iontophoretic delivery of methotrexate. Initial screening studies evaluated the effect of ionic strength and donor concentration. A response surface model was then used to evaluate current density and time of application.

INTRODUCTION: Methotrexate (MTX) is a folic acid antagonist with antineoplastic activity that is useful in the treatment of psoriasis and rheumatoid arthritis. It is administered by oral or parenteral route for the treatment of psoriasis. When administered systemically over prolonged periods, it may produce side effects like nausea, vomiting, fatigue, anemia headache, leukopenia, thrombocytopenia and hepatic toxicity. Iontophoretic delivery of MTX can reduce such side effects by delivering it directly to the diseased psoriatic skin rather than systemically. Methotrexate has three pKa's (5.6, 3.8, and 4.8); it is negatively charged at physiological pH and was thus delivered by cathodal iontophoresis by means of electrorepulsion. MTX delivery was first studied at various buffer strengths and at different drug concentrations. Once the optimum ionic strength and drug concentration was selected, a fractional factorial design was used to study the effect of current density and time of application.

EXPERIMENTAL METHODS: The delivery of MTX under 30 mins of iontophoresis (0.4 mA/cm^2) was studied at buffer strengths 0.05-0.5 M and drug concentrations 10-20 mg/ml. The effect of current density and time of application on the delivery of MTX is studied by optimizing the full-factorial design. The current density (X_1) and time of application (X_2) are the independent factors chosen for the factorial design with 4 and 5 levels, respectively in the range of 0.05 -0.5 mA (X_1) and 10-120 mins (X_2).

In vitro iontophoretic experiments ($n \geq 3$) were performed using freshly excised hairless rat skin mounted on vertical Franz diffusion cells with stratum corneum facing towards the donor chamber. The donor compartment contained 15 mg/ml of MTX in phosphate buffer of pH 7.4 (0.25 M) and the receptor compartment contained phosphate buffer of pH 7.4 (0.25 M) with 75 mM NaCl.

Expt#	X_1	X_2
1	-1.0	-1.0
2	-1.0	1.0
3	1.0	0.0
4	1.0	1.0
5	-0.3333	-0.5
6	1.0	-1.0
7	-1.0	0.0
8	0.3333	1.0

Table 1

A silver-silver chloride electrode (cathode) was placed in the donor chamber and silver wire (anode) was placed in the receptor compartment. The current density and time application was applied according to the variables in Table 1. Samples were taken at periodic intervals and were analyzed by HPLC, using YMC RP 18 column. Mobile Phase was composed of monobasic sodium phosphate (10%) and Tris HCl buffer (90%). Flow rate was 1.5 ml/min and detection wavelength was 303 nm.

RESULTS AND DISCUSSION: The cumulative amount of MTX delivered across hairless rat skin increased with decrease in ionic strength of the buffer (Figure 1). Phosphate buffer of pH 7.4 and ionic strength 0.25 M was selected to avoid the changes in pH observed when 0.05 M buffer was used. The amount of drug delivered increased with increase in MTX drug concentration from 10 to 15 mg/ml at 0.25 M buffer strength (Figure 2). However, delivery at 15 and 20 mg/ml is not statistically different; this might be due to the saturation of the boundary layer at higher concentrations.

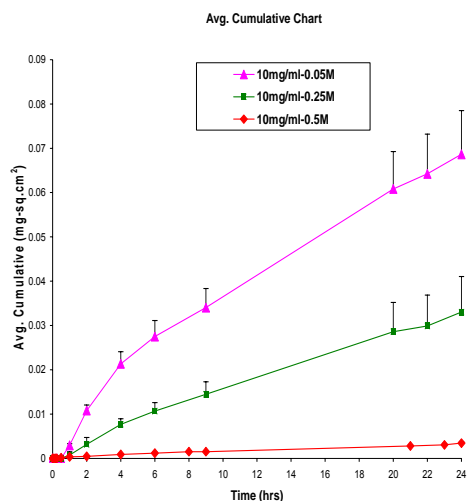


Figure 1

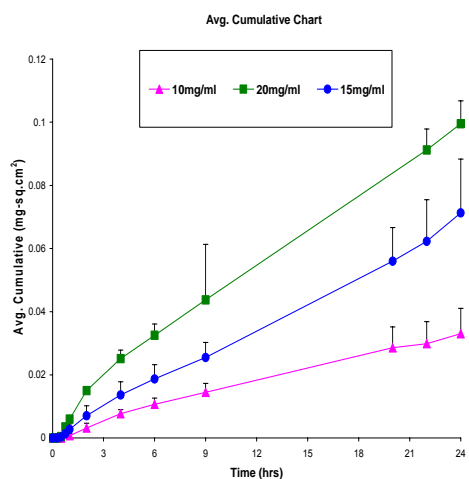


Figure 2

The experimental data of the fractional factorial design (Table 1) is plotted as seen in Figure 3 and the response surface plot is shown in Figure 4. The factorial design shows that with the increase in current density and time of application, the cumulative amount of MTX delivered also increased. However, for 10 min iontophoresis, an increase in current density from 0.05 to 0.5 mA did not show a statistically significant increase. An increase in time of application from 10-120 mins at 0.05 mA did not show any enhanced delivery of the drug.

The predictions of the model have been verified by performing an experiment in the experimental region with current density 0.4mA and ITP for 30mins. The cumulative amount of drug delivered was found to be in between the lower and upper 95% confidence level, thus establishing the validity of the model.

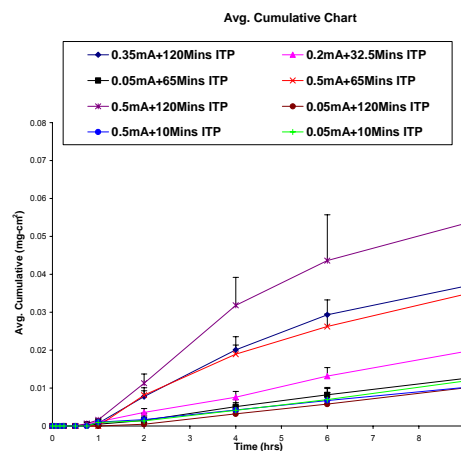


Figure 3

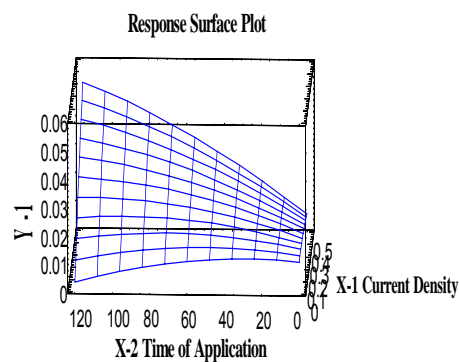


Figure 4

CONCLUSION: Screening studies were first used to select the buffer strength (0.25 M) and drug concentration (15 mg/ml). An increase in time of current application and/or current density led to increased delivery of MTX across the skin only for higher level settings. The optimal flux of about 0.6 $\mu\text{g}/\text{cm}^2\text{-hr}$ was obtained.

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ACKNOWLEDGEMENTS: We would like to thank Transport Pharmaceuticals for funding this project.