行政院國家科學委員會專題研究計畫　成果報告

DFO 經皮給藥的可行性研究

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摘要

海洋性貧血病人需長期接受輸血以維持生命，然而長期輸血容易導致病人體內三價鐵離子含量過高而產生鐵中毒的現象，鐵中毒慣例上採用 deferoxamine mesylate(Desferal®, DFO)連續式點滴或皮下注射以螯合治療，但病患容易因為疼痛而產生排斥感，使治療效果不佳，所以我們希望能夠改變藥物劑型，企圖以經皮給藥的方式來取代注射治療，本實驗的目的即是評估將 DFO 製成貼劑貼在皮膚上給藥的可行性，將選擇基質式經皮吸收系統，使 DFO 能穿過皮膚，藉以設計 DFO 貼片。此貼片希望能夠以一定傳送速率讓藥穿過皮膚到達循環系統，而達全身性治療效果。本實驗係以商用感壓膠為基質，探討 DFO 在其中的藥物釋放情形，以開發為經皮吸收貼劑。

關鍵字：海洋性貧血、Desferal®、經皮給藥系統

ABSTRACT

The goal of this study is to help thalassemia patients, who chronically require blood transfusions to keep alive. However, such long-term transfusions can easily lead to a build-up of trivalent iron and produce an iron overload condition. To treat iron overload, the patients usually receive intravenous or subcutaneous deferoxamine mesylate (DFO) regularly. But, because of the pain the patients may resist taking drug, so the effects of treatment are not very good. Consequently, we hope to be able to change the method of delivering DFO—we want to see if we can replace the injection method with transdermal drug delivery. The preliminary goal of the study, therefore, is to assess the feasibility of designing and fabricating a DFO patch using an adhesive dispersion-type transdermal drug delivery system. It is hoped that it can let the drug pass through the skin at a fixed rate of speed and reach the circulation system, from where it can spread its therapeutic effect throughout the body. In this research, we choose the commercial pressure sensitive adhesives to be the drug reservoirs and observe the release profile of DFO in the adhesives in order to develop and design transdermal patchs.

Keywords: thalassemia, Desferal®, transdermal drug delivery system

Introduction

Desferrioxamine (DFO) (Desferal®) is the drug of choice for removing iron from human subjects. Although DSO has been available for the treatment of iron load for a long time, the number of studies addressing the DFO permeability through skin is surprisingly few. In this work, transdermal administration of DFO was investigated as therapy for removing iron. The advantages of transdermal DFO include: (a) the convenience and increased compliance of a dosage form, (b) a constant plasma level, (c) the elimination of infection, and (d) no pain.

Materials and methods

Materials

DFO was obtained from Novartis Pharmaceuticals Corp (East Hanover, NJ). Pressure-sensitive acrylic adhesives were obtained from the National Starch and Chemical Company (Bridewater, New Jersey). All other chemicals and solvents were of analytical-reagent grade.

Permeation experiments

Porcine skin from the abdominal and breast area with the lower density of hair follicles was obtained from the local slaughterhouse. After removing subcutaneous fat tissue, samples (2 mm thickness) of 44 mm diameter (n=4 for each experiment) were punched and mounted to a two-chamber diffusion cell with a volume of 36 ml each. Phosphate-buffered saline (PBS) well-stirred and thermoregulated at 37°C served as receptor fluid. The drug solution containing 10 mg/ml DSO in PBS, applied to the skin surface, was placed in the donor compartment. At each predetermined time interval, 0.2 ml of receptor solution was sampled and replaced immediately with the same volume of drug-free PBS. The concentration of DFO in the sample was analyzed by a Waters HPLC system, equipped with a Waters 510 HPLC pump, a Waters 510 solvent delivery system, a Waters 2487 dual λ absorbance detector operating at a wavelength of 210 nm, and a 3.9 mm by 15 cm Symmetry C_{18} column (waters). The mobile phase consisted of 76% 10mM NaH_2PO_4 (pH 3.0), 17% methanol, and 7% acetonitrile at a flow-rate of 1.0 ml/min, and all analyses were conducted at ambient temperature [1]. Under these conditions, the retention time was 3.2 min. Each experiment was repeated four times and the results were expressed as the mean of the four results.

Results

Figure 1 shows the concentration of DFO permeated across porcine skin from 9.49 mg/ml solution in the receiver cell as a function of time. In vitro permeation test is widely used because of its simplicity and reproducibility. The total amount permeated with time can be easily calculated by simply multiplying the receiver cell volume. The preliminary permeation experiment indicated that DFO is skin-permeable.

Figure 2 shows the in vitro release profiles of DFO from four pressure-sensitive acrylic adhesives over 24 h. All four pressure-sensitive acrylic adhesives showed a burst effect during the first two hours of the assay and then plateaued. However, solely matrix prepared with DURO-TAK 387-2054 showed a higher drug release rate. The explanation of this is likely that drug diffusion through matrix was influenced by the drug-polymer interaction [2]. The higher release rate of DFO from DURO-TAK 387-2054 led to prove that it is appropriate for transdermal DFO delivery.

One of the important parameters that design transdermal drug delivery system is drug concentration in the matrix. Figure 3 shows the effect of drug loading in DURO-TAK 387-2054 on the amount of DFO permeated across porcine skin as a function of time. Theoretically, the flux of drug increases as the drug loading increases due to higher driving force. However, the permeation profile of 5% drug loading is higher than those of 10% and 15% drug loading. The unusual phenomenon may be attribute to the drug crystallization in the matrix [3].

The mass balance equation that describes the evolution of drug concentration in the receptor chamber is given by

錯誤! 尚未定義書籤。 (1)

where C_d and C_r are concentrations of the drug in the donor and receptor chambers, respectively. A is the effective transport area for the drug, L is the thickness of the skin, V is the volume of each chamber and D is the drug diffusion coefficient in skin. Using Equation (1) and the data in Figure 3, the diffusivity and the area for TDDS can be calculated and tabulated in Table 1.

Conclusions

Patches may be helpful for long term administration of DFO because they can keep the desired concentration of drug in the body without non-continuous night administration. However, Table 1 shows the area for TDDS is too high. Therefore, it needs further investigation to modify the TDDS system and animal studies will be performed in the future.

References

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Figure 1

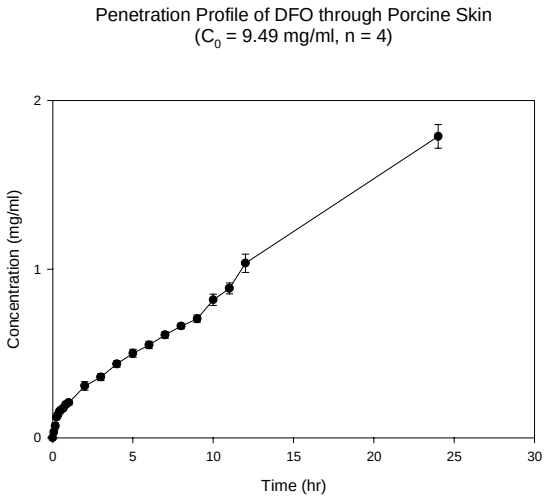

Figure 2

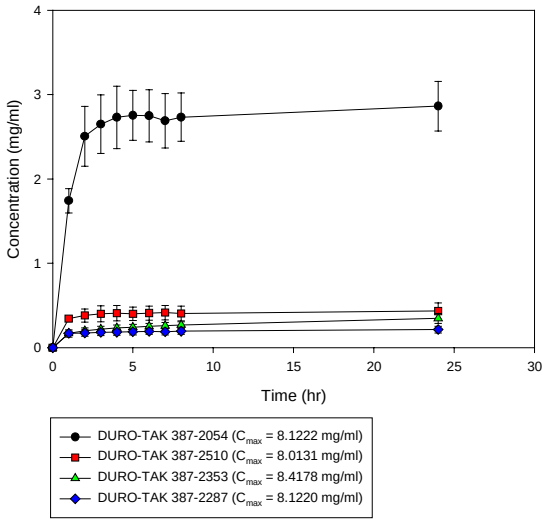

Figure 3

Release Profiles from 5%, 10% and 15% TDDS through Porcine Skin (n = 4)

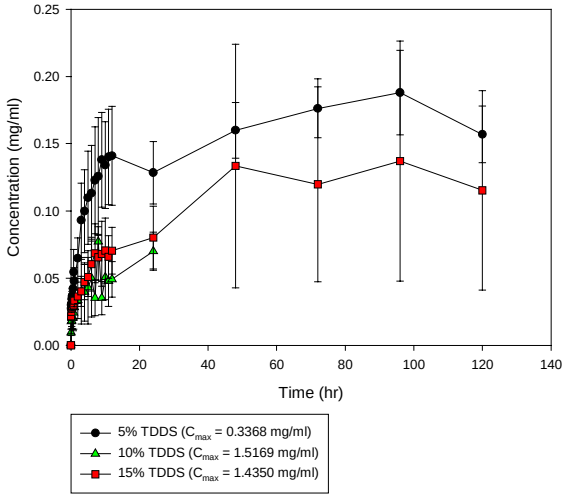

Table 1

Time (hr)	Flux (mg/cm^2·hr)	Diffusivity (cm^2/hr)	Area (cm^2/kg)
6	0.1093	0.3245	19.0589
8	0.0912	0.2707	22.8486
12	0.0682	0.2023	30.5653
24	0.0398	0.1182	52.3188