Numerical Modelling of Transdermal Delivery from Matrix Systems: Parametric Study and Experimental Validation with Silicone Matrices

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ABSTRACT: A model is presented for transdermal drug delivery from single-layered silicone matrix systems. The work is based on our previous results that, in particular, extend the well-known Higuchi model. Recently, we have introduced a numerical transient model describing matrix systems where the drug dissolution can be non-instantaneous. Furthermore, our model can describe complex interactions within a multi-layered matrix and the matrix to skin boundary. The power of the modelling approach presented here is further illustrated by allowing the possibility of a donor solution. The model is validated by a comparison with experimental data, as well as validating the parameter values against each other, using various configurations with donor solution, silicone matrix and skin. Our results show that the model is a good approximation to real multi-layered delivery systems. The model offers the ability of comparing drug release for ibuprofen and diclofenac, which cannot be analysed by the Higuchi model because the dissolution in the latter case turns out to be limited. The experiments and numerical model outlined in this study could also be adjusted to more general formulations, which enhances the utility of the numerical model as a design tool for the development of drug-loaded matrices for trans-membrane and transdermal delivery. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:2366–2375, 2014

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INTRODUCTION

Modelling of transdermal drug delivery is a much researched topic.[1–8] Investigators have mainly focused on detailed modelling of the skin properties[9,10] and the interaction between skin and drug,[11–13] but fewer studies have included the formulation properties in the model.[14,15] Matrix type formulations are common types of delivery systems used for transdermal delivery. In such systems, the drug release is controlled by the diffusion of the drug and the dissolution of drug particles suspended in the matrix. In his seminal work, Higuchi[16] proposed a model to describe the release of drugs from transdermal formulations such as creams and ointments. The model was later adapted to describe release from solid matrix systems.[17] This model is now commonly used in textbooks to describe release from matrix systems and is often simply referred as the "Higuchi equation." In this model, the cumulative release is given by a simple closed form expression derived from an analytic solution, and relating the amount of drug released per unit area of matrix to the diffusion coefficient for the drug in the matrix, the total amount of drug in a unit volume of the matrix, and the solubility of drug in the polymer matrix.

To arrive at this expression, it is necessary to make certain assumptions about the system, such as it being semi-infinite, having homogenous initial distribution and instantaneous dissolution of the drug. Analytical solutions, usually, can only describe the steady-state or pseudo-steady-state situation. Numerical approach, such as finite element (FE), finite volume (FV) and finite difference (FD) methods, is now commonly used to solve complex mathematical problems, expressed in terms of differential equations when analytical solutions cannot be found. Numerical models form an integral part of the research and development in many fields because of the significant advances in computer simulation technology. Such models can, for example, be constructed from routines in available software packages. A few publications have described numerical models of inert matrix systems.[18–20] We have introduced a mathematical model based on previous work[21] to describe multi-layer matrix systems with inhomogeneous initial distribution of the drug.[22] Drug release and dissolution processes were described in terms of two coupled nonlinear partial differential equations (PDEs), based on the Noyes–Whitney equation[23] and the Fick's diffusion equation.[24]

The corresponding numerical model, based on a FE approach and implemented in Matlab,[25] allowed for a limited dissolution rate. The model was transient and did not require a pseudo-steady-state approximation. It was validated against experimental data for drug release from silicone matrices containing diclofenac sodium and ibuprofen sodium as embedded model drugs. The model applies to drug-incorporated silicones. These types of systems are used in various types of applications such as birth control implants and transdermal patches.

In the current work, we investigate the original problem considered by Higuchi, namely the combination of drug delivery matrix and skin. The previous model only considered the release from a layered matrix, but in the current model, the barrier function of the skin or some model membrane is included

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in the model. The mathematical model is the same as in our previous work with the important addition of allowing different solubility values between layers which result in discontinuous jumps in drug concentration (partition) across the interface between such layers. To deal with such discontinuities, the numerical model has to be modified. The model remains transient and could therefore be used to predict lag times in addition to the drug flux for transdermal delivery.

Experimental evaluation and validation of the model was carried out with combination of silicone matrices and nude mouse skin or silicone membrane. This included matrices with a fast-dissolving drug (ibuprofen sodium) and a slow-dissolving drug (diclofenac sodium). The evaluation of the model was carried out in such a way that the prediction power of the model could be challenged. Modelling was used to find parameter values for the matrix systems, based on release studies, and for the membranes by an investigation of trans-membrane delivery from donor solutions. The parameter values found for the individual parts of the system could then be compared with the parameter values of the combined systems.

EXPERIMENTAL METHODS

Materials

Silicone elastomer MED-4901 was obtained from NuSil (Carpinteria, California) and kleptose hydroxypropyl-β-cyclodextrin (HPβCD) from Roqette (Lestrem, France). Diclofenac sodium, ibuprofen sodium, dimethylpolysiloxan 20 cSt, and HPLC-grade acetonitrile were purchased from Sigma–Aldrich (St. Louis, Missouri). Sodium hydroxide and potassium dihydrogen phosphate were purchased from Merck & Company, Inc. (Whitehouse Station, New Jersey). Acetic acid was purchased from Riedel-deHaën (AG Seelze, Germany). Deionised water for the HPLC mobile phase was produced with a Milli-Q purification system (Millipore A/S, Copenhagen, Denmark).

HPLC Analysis

HPLC analyses were carried out using a Dionex Ultimate 3000 HPLC, HPG-3400 pump with degasser, WPS 3000 TSL autosampler, TCC 3100 thermostatted column compartment, PDA 3000 detector and Chromeleon chromatography workstation (Thermo Scientific, Sunnyvale, CA). OnyxTM Monolithic C18 column (4.6 × 100 mm^2, 5 μm, Phenomenex, Torrance, CA) with a flow rate of 1.5 mL/min was used. Mobile phase for diclofenac consisted of 65% acetonitrile, 34.6% water and 0.4% acetic acid. The detection wavelength was 281 nm, the retention time average was 2.10 min and the detection limit was 0.1 μg/mL. Mobile phase for ibuprofen consisted of 60% acetonitrile, 39.6% water and 0.4% acetic acid. The detection wavelength was 230 nm, the retention time average was 1.90 min and the detection limit was 3 μg/mL.

Preparation of Silicone Matrix-Type System

Silicone elastomer MED-4901 is supplied as a two-component kit (parts A and B). Part A contains a platinum catalyst and part B contains cross-linker and cure inhibitor. Part A and part B were combined in a 1:1 ratio and mixed with strained drug (125 μm sieve) in a speed mixer (Planetary Mixer/Deaerator Mazerustar) for 100–200 s. Subsequently, the mixtures were poured into a circular aluminium mould (diameter 170 mm and thickness 2 mm). The mixtures in the moulds were degassed under vacuum for 1 h and then the mould was closed with a lid (where excess silicone was forced out through openings in the lid). The moulds were placed in a pre-heated oven (120°C) for 2–4 h to cure the silicone mixture. The silicone elastomer matrix systems (silicone membranes) were stored at room temperature before use. Drug loadings are presented as percentage total weight of MED-4901, 1:1 mix of part A and B (w/w).

In Vitro Release Studies from Drug-Loaded Silicone Matrices and Trans-Membrane Studies

Silicone membrane matrices were cut into small circles (diameter 32 mm). *In vitro* release studies were conducted with vertical Franz diffusion cells (membrane surface area of 1.77 cm^2 and a cell volume of 12 mL). When drug-loaded silicone matrices were tested, the donor chamber was not used in the Franz cell setup, but they were used in the trans-membrane donor solution studies. When the donor phase was not (see Fig. 1) used, a plexiglass plate was placed on the top of the membrane to prevent the diffusion of air through the drug-containing membrane. Phosphate buffer, pH 7.4 with 2.5% (w/v) HPβCD, was used as the receptor medium, with stirring at 400 rpm. Samples (600 μL) were withdrawn from the receptor compartment at pre-determined time intervals, and replaced with an equal volume of fresh medium. Samples were analysed by HPLC to determine the quantity of drug that had been released from the silicone matrix membrane. Calculations because of the dilution

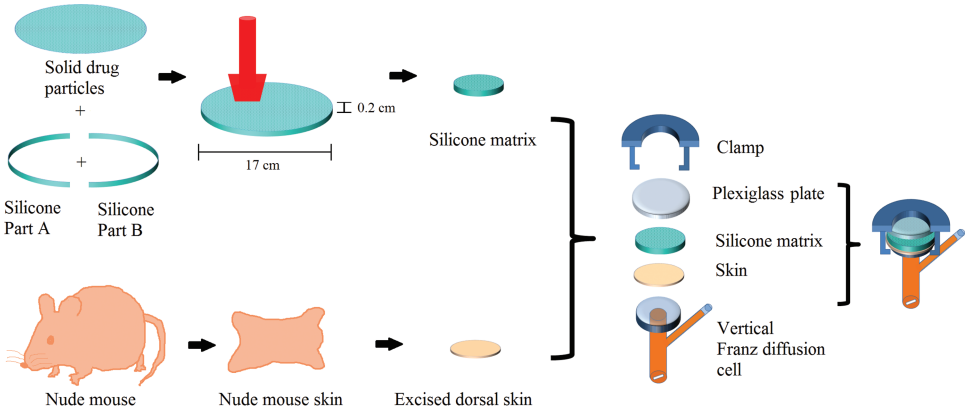

Figure 1. Unconventional setup of Franz diffusion cell, using a plexiglass plate instead of the usual donor.

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