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Numerical modelling and experimental investigation of drug release from layered silicone matrix systems

Bergthóra S. Snorradóttir [a], Fjóla Jónsdóttir [b], Sven Th. Sigurdsson [b], Freygardur Thorsteinsson [c], Már Másson [a,*]

[a] Faculty of Pharmaceutical Science, University of Iceland, Hofsvallagata 53, IS-107 Reykjavik, Iceland
[b] Faculty of Industrial Engineering, Mechanical Engineering and Computer Science, University of Iceland, Hjardarhagi 2-6, IS-107 Reykjavik, Iceland
[c] Össur hf., Grjóthálsi 5, IS-110 Reykjavik, Iceland

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ABSTRACT

Medical devices and polymeric matrix systems that release drugs or other bioactive compounds are of interest for a variety of applications. The release of the drug can be dependent on a number of factors such as the solubility, diffusivity, dissolution rate and distribution of the solid drug in the matrix. Achieving the goal of an optimal release profile can be challenging when relying solely on traditional experimental work. Accurate modelling complementing experimentation is therefore desirable. Numerical modelling is increasingly becoming an integral part of research and development due to the significant advances in computer simulation technology.

This work focuses on numerical modelling and investigation of multi-layered silicone matrix systems. A numerical model that can be used to model multi-layered systems was constructed and validated by comparison with experimental data. The model could account for the limited dissolution rate and effect of the drug distribution on the release profiles. Parametric study showed how different factors affect the characteristics of drug release. Multi-layered medical silicone matrices were prepared in special moulds, where the quantity of drug in each layer could be varied, and release was investigated with Franz-diffusion cell setup. Data for long-term release was fitted to the model and the full depletion of the system predicted. The numerical model constructed for this study, whose input parameters are the diffusion, effective dissolution rate and dimensional solubility coefficients, does not require any type of steady-state approximation. These results indicate that numerical model can be used as a design tool for development of controlled release systems such as drug-loaded medical devices.

1. Introduction

Medical devices that can release drugs or other bioactive compounds are of interest for a variety of applications. Controlled drug release can be either the only function of the device, such as, for trans-dermal drug delivery and birth control implants (Florence and Attwood, 1998; Brook, 2000), or the drug release can be used to enhance the function of devices, such as catheters (Kohnen et al., 1998, 2003), voice prostheses (Buijssen et al., 2007) and cochlear implants (Zou et al., 2008). These types of devices are typically prepared from medical silicone or other non-erodible polymer that forms solid matrix for the dissolved drug and drug particles. Drug-loaded, polymer-based devices must release the drug at a certain rate over a given period of time, while maintaining the shape and material properties required for the primary function of the device. Achieving these goals in an optimal fashion is challenging if it relies solely on traditional experimental work. Accurate modelling complementing experimentation is therefore desirable, as it will allow rapid evaluation of parameters and subsequent validation of a select set of promising cases.

A number of mathematical models for drug release from matrix systems have been proposed over the years (Higuchi, 1961, 1963; Wu and Zhou, 1998; Frenning, 2003, 2011; Frenning et al., 2005; Cabrera et al., 2006; Cabrera and Grau, 2007; Siepmann and Siepmann, 2008; Helbling et al., 2011a). Two theoretical models have typically been applied for non-erodible matrices such as silicone, depending on the relative magnitudes of drug concentration and solubility in the matrix. If the drug concentration is low enough for all of the drugs to be dissolved uniformly, the release rate can be determined by the well-known Fick's second law (Crank, 1979). In the case of higher drug concentrations, or lower solubility, both dispersed and dissolved drugs exist in the matrix at the same time. The Higuchi model (Higuchi, 1961, 1963) is commonly used for analysis of experimental data and has proven to give good results when the initial drug concentration is much

* Corresponding author. Tel.: +354 525 4463; fax: +354 525 4071.
E-mail address: mmasson@hi.is (M. Másson).

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higher than the solubility limit. In that case a pseudo-steady state approximation is used and a dissolution–diffusion moving front is assumed.

Helbling and co-workers recently proposed a model that is adjusted for the geometry of single and two-layer vaginal rings (Helbling et al., 2011a,b).With the assumptions that the models have instantaneous dissolution and uniform distribution of the drug, and therefore, do not apply when drug dissolution is a limiting factor. Furthermore, it is of limited use for the design of medical devices when the drug distribution is non-uniform and when the entire drug will be released, such as in the case of permanent implants.

The current work focuses on matrix systems with inhomogeneous distribution of the drug. A mathematical model based on the work by Frenning (2003) and Frenning et al. (2005)) was modified to apply to layered silicone polymer-based drug release matrices. Drug release and dissolution processes were described in terms of two coupled nonlinear partial differential equations (PDEs), which are a combination of the Noyes–Whitney equation (Noyes and Whitney, 1897) and Fick's diffusion equation (Crank, 1979), for a slowly dissolving drug release. The corresponding numerical model implemented in Matlab (Matlab, 2010) allowed for a limited dissolution rate and did not require pseudo-steady state approximation. The model was applied to a set of specific multi-layer cases. Finally the model was verified with comparison to experimental data from multi-layered silicone matrix systems. For this purpose specialised moulds for preparing planar silicone matrices, allowing embedding of the drugs into well-defined thin layers, were designed. Silicone membranes, with layers containing embedded drug particles at given concentrations, were prepared, using both ibuprofen sodium and diclofenac sodium. The release data were compared to the prediction of the model. The numerical model can be used synergistically with traditional experimentation in the future to design efficient controlled release system with inhomogeneous distribution of the drug.

2. Materials and methods

2.1. Materials

Silicone elastomer MED4-4220 was obtained from NuSil (Carpinteria, USA) and Kleptose Hydroxypropyl-β-cyclodextrin (HPβCD) from Roqette (Lestrem, France). Diclofenac sodium (Na-diclofenac), ibuprofen sodium (Na-ibuprofen), dimethylpolysiloxan 20 cSt and High-performance liquid chromatography (HPLC) grade acetonitrile were purchased from Sigma–Aldrich (St. Louis, MO, USA), sodium hydroxide and potassium dihydrogen phosphate were purchased from Merck & Co., Inc. (Whitehouse Station, NJ, USA). Acetic acid was purchased from Riedel-deHaën (AG Seelze, Germany). Deionized water for the HPLC mobile phase was obtained by a Milli-Q purification system (Millipore A/S, Copenhagen, Denmark). All other chemicals were of the highest analytical grade.

2.2. Preparation of multi-layered silicone matrix-type system

Silicone elastomer MED4-4220 is supplied as a two-component kit (parts A and B). Part A contains a platinum catalyst and part B a cross-linker and cure inhibitor. Each layer was prepared separately with the exception of when layers contained the same concentration of drug, at which point the layers could be prepared simultaneously. Layers were prepared by combining part A and part B in a 1:1 ratio with or without strained drug (125 μm sieve) and thoroughly mixed with a spatula. The mixtures were degassed under vacuum for 5–15 min. Each layer was spread onto an aluminium mould (Fig. 1 (and Supplementary Fig. S1)), and evenly dispersed with scrapers, before being placed the mould in a pre-heated oven (100–120 °C) for 5–10 min to cure the silicone mixture. This was repeated one layer after another. The multi-layered silicone elastomer matrix systems (silicone membranes) were stored at room

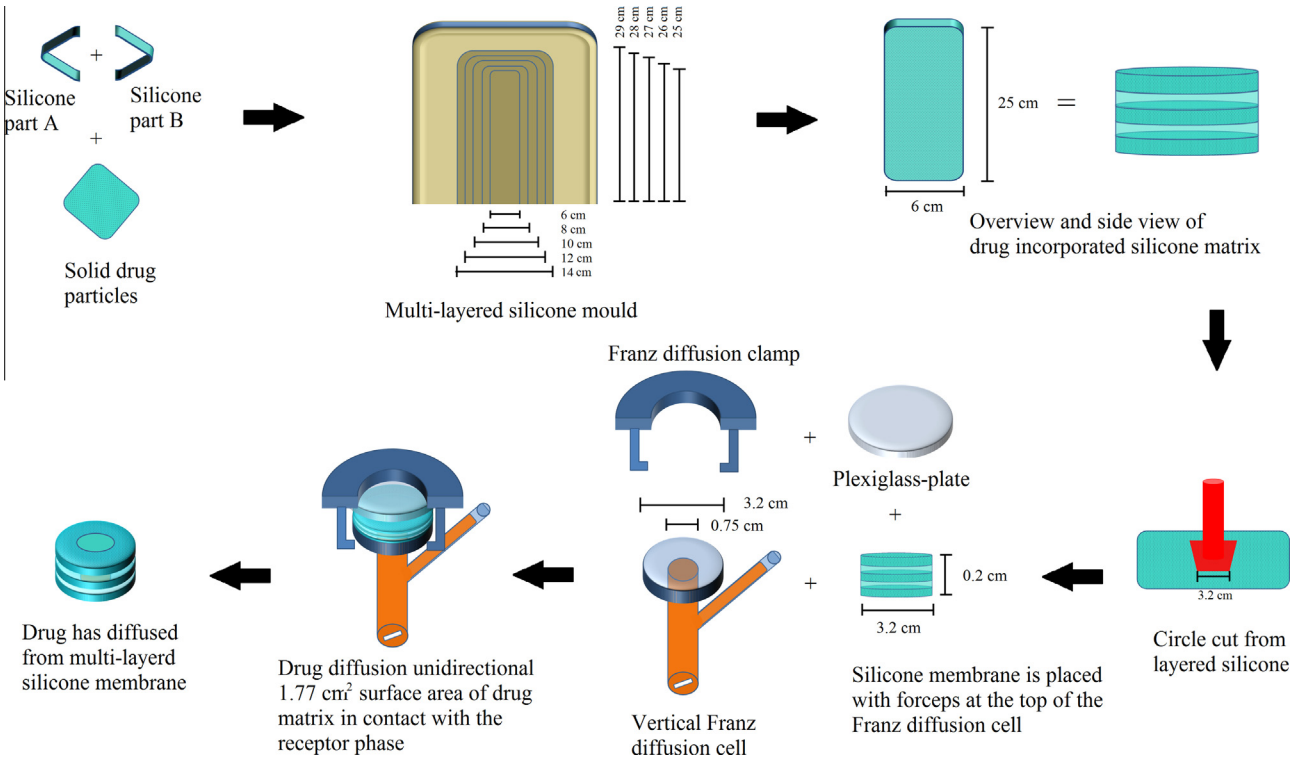

Fig. 1. A schematic figure (not proportional) of preparation of multi-layered drug containing silicone membrane and drug release study. The silicone mixture was formed from two parts (A and B) combined with drug. This mixture was poured on multi-layered mould, one layer at time, and the mould was placed in a pre-heated oven to cure each layer. A fully cured multi-layered silicone was cut with a puncher to form circular discs. The disc was fixed on Franz diffusion cell for the release.