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Solute permeability of elastomeric films containing dispersed swellable hydrophilic particles: A composite material approach

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ABSTRACT

Theophylline permeation experiments in poly(dimethylsiloxane) (PDMS) films modified by various amounts of a hydrophilic additive, polyethylene glycol (PEG) of molecular weight 3000 (present in the form of dispersed swellable spherical particles), were performed at 37 °C. The permeability coefficients derived from these data, increase systematically from a value of $P = 2.0 \times 10^{-10}$ cm^2/s for pure PDMS to $P \sim 15 \times 10^{-10}$ cm^2/s for PDMS containing 20% w/w PEG, in line with the corresponding increase of the measured water uptake capacity of the films. The data were analyzed on the basis of the Maxwell model for binary composite materials consisting of a highly permeable swollen PEG phase dispersed in a continuous PDMS phase of a much lower permeability to theophylline. The requisite parameters for application of the model were derived from experimental information obtained from this work or from the literature. A good agreement between model and experimental results was found up to volume fractions of swollen PEG phase, well above those characterizing dilute dispersions. Effective P values were also derived from theophylline release kinetics from the corresponding matrices containing dispersed drug. Permeability coefficients from both types of experiments exhibit the same trends with increasing PEG content in the PDMS samples. Small differences in the absolute values of P are also discussed.

1. Introduction

The discovery that PDMS tubing is permeable to low MW organic molecules [1] has led in the 1970's to the first PDMS-based devices for the controlled release of lipophilic low MW steroids [2]. Since then, PDMS has been employed as controlled-release carrier for a broader range of bioactive substances of varying polarity and/or higher MW. To achieve the desired permeation properties for a specific drug or class of drugs, the hydrophobic PDMS polymer is chemically modified or physically mixed with hydrophilic moieties or compounds, respectively.

Hydrophilic additives may act in different ways during the release process, depending on their osmotic properties and their weight content in the matrix. A well-studied mechanism is the microscopic cracking of PDMS matrix produced by the addition of particles of inorganic salts, that attract high amounts of water during the release process. At high loads of the osmotic additive, this mechanism may lead to a network of cracks filled with water, through which the release of the drug is strongly accelerated [3,4].

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Additives of milder osmotic action, such as sugars and polyethylene glycols [5–7], may be leached out of the matrix during the release process, leaving behind pores or channels filled with water (act as a "channeling agent" or "pore former") or may exist as a distinct swollen phase, contributing to the solute transport. In both cases, low additive contents accelerate the release process only moderately, since the swollen areas in the matrix are isolated.

In a previous publication we studied the release profiles of three xanthine derivatives from matrices of pure PDMS, and the effect of incorporating 10% w/w polyethylene glycol (PEG-3000) in the matrix [7]. In all three cases, the moderate increase in release rates upon inclusion of PEG in the PDMS matrix, pointed to the behavior of a two-phase system, consisting of a PDMS continuous phase characterized by a much lower permeability than that of the dispersed, swollen PEG phase.

Here we proceed to test this hypothesis by theophylline (TPL) permeation measurements through PDMS films containing various amounts of PEG-3000. The permeability coefficients, P, derived from these measurements are analyzed on the basis of the Maxwell model for binary composite materials. The Maxwell equation, or similar mixing rules [8], have been applied to analyze gas permeation in immiscible polymer blends [9,10], in polymer films containing highly selective fillers [11,12] and in block and graft copolymers [13]. It has also been applied to the permeability properties of salt-depleted cellulose acetate matrices [14] but to our knowledge, there is rare, if any, report on the application of the Maxwell model for rationalizing the enhancement of drug permeability upon inclusion of hydrophilic additives with mild osmotic action in hydrophobic elastomeric matrices. The P values derived from permeation data are also compared with the corresponding values derived from drug release kinetic data.

2. Experimental

2.1. Materials and film preparation

Poly(dimethylsiloxane) (PDMS) was kindly supplied by Momentive (USA) as a two-component kit (RTV 615 type). Part A contains a vinyl poly(dimethylsiloxane) prepolymer, and part B is the crosslinker containing hydrosilane groups in the poly(dimethylsiloxane) chains. Crosslinking of PDMS occurs via an addition reaction between vinyl and –SiH groups, in the presence of a Pt catalyst. Polyethylene glycol (PEG) of MW = 3000 g/mol and density d = 1.21 g/cm^3 was purchased from Merck (Germany). Dichloromethane was of analytical reagent grade. Theophylline (TPL) C7H8N4O2 (1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurine) of MW = 180.2 g/mol, d = 1.47 g/cm^3 and water solubility 11.81 mg/cm^3 at 37 °C was purchased from Acros Organics (Belgium).

Preparation of PDMS films containing 0–20% w/w PEG has been described in detail elsewhere [15]. Briefly, to promote dispersion of PEG in the viscous RTV prepolymer mixture, the proper amount of PEG (0.055–1.1 g) was first dissolved in 1 ml of dichloromethane and then added to approximately 5.5 g of A and B mixture of composition A:B = 10:1 w/w, under mechanical stirring. The mixture was cast on a glass plate and cured at 100 °C for 1 h, resulting in free-standing films. PDMS–PEG matrices containing 0.07 g TPL/g PDMS were similarly prepared by adding to the, prior to curing, polymeric mixture the appropriate amount of TPL. The specific TPL load was adequately high to ensure supersaturated matrices.

Film thicknesses, L, measured by means of a micrometer reading to 1 μm, were in the range 90–250 μm.

In what follows, the PDMS–PEG films and matrices are designated by a number indicating the incorporated amount of PEG, in % by wt, in any particular film.

2.2. Thermal, mechanical and morphological characterization

Information on the physical state of theophylline within the polymeric matrix was derived from DSC measurements of the drug's melting endotherm during heating of the matrix samples. A 2920 Modulated Differential Scanning Calorimeter–MDSC (TA Instruments, USA) was used to perform heating runs on 10 mg samples of drug-loaded matrices from ambient temperature up to the TPL melting temperature at a heating rate of 5 °C/min, in a nitrogen atmosphere.

The Young modulus of films was determined from stress–strain tests, at 20 ± 2 °C and 65 ± 5% relative humidity, with a Tensilon UTM-II-20 instrument (Toyo Baldwin Co., Ltd., Japan). Film samples of lateral dimensions 1 × 20 mm^2 and thickness 100 μm < L < 250 μm were tested at a constant elongation rate of 20 mm/min and a grip separation of 10 mm. At least five samples from each type of film were tested.

A JEOL 7401F Field Effect Scanning Electron Microscopy (FESEM) was used to examine fractured cross-sections of films.

2.3. Permeation experiments

Permeation experiments were performed in a two-compartment side by side cell. Films were equilibrated in water at 37 °C, weighed for water uptake determination, and then mounted between the donor compartment containing a TPL solution of c_o = 6 mg/cm^3 and the receptor compartment containing distilled water. The volume of each compartment was 3 ml and the exposed film area was A = 0.785 cm^2. The apparatus was maintained at 37 °C by circulating constant-temperature water through the jackets surrounding each compartment. The solutions in both compartments were magnetically stirred. Samples of volume 3 ml were periodically withdrawn from the receptor compartment and drug concentration was determined by UV–VIS spectroscopy at 271 nm. The amount of solution removed was each time replaced by pure water.

The slope of the cumulative amount of TPL, Q_t, vs time at steady state conditions, can be used to calculate the permeability coefficient P according to