International Journal of Pharmaceutics 515 (2016) 467–475

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Controlled drug release from hydrogels for contact lenses: Drug partitioning and diffusion

A.F.R. Pimenta[a,b], J. Ascenso[a], J.C.S. Fernandes[a], R. Colaço[b], A.P. Serro[a,c], B. Saramago[a,*]

[a] Centro de Química Estrutural, Instituto Superior Técnico, University of Lisbon, Av. Rovisco Pais, 1049-001 Lisbon, Portugal
[b] IDMEC, Departmento de Engenharia Mecânica, Instituto Superior Técnico, University of Lisbon, Av. Rovisco Pais, 1049-001 Lisbon, Portugal
[c] Centro de Investigação Interdisciplinar Egas Moniz, Instituto Superior de Ciências da Saúde Egas Moniz, Quinta da Granja, Monte de Caparica, 2829-511 Caparica, Portugal

ARTICLE INFO

Article history:
Received 24 June 2016
Received in revised form 21 October 2016
Accepted 22 October 2016
Available online 24 October 2016

Chemical compounds studied in this article:
Chlorhexidine diacetate monohydrate (PubChem CID: 9562059)
Levofloxacin (PubChem CID: 149096)
Diclofenac sodium (PubChem CID: 5018304)
Poly-hydroxyethylmethacrylate (PubChem CID: 13360)
3-Tris(trimethylsilyloxy)silylpropyl 2-methylprop-2-enoate (PubChem CID: 123371)
Poly(vinylpyrrolidone) (PubChem CID: 6917)

Keywords:
Drug release
Contact lens
Hydrogel membrane
Partition coefficient
Diffusion coefficient

ABSTRACT

Optimization of drug delivery from drug loaded contact lenses assumes understanding the drug transport mechanisms through hydrogels which relies on the knowledge of drug partition and diffusion coefficients. We chose, as model systems, two materials used in contact lens, a poly-hydroxyethylmethacrylate (pHEMA) based hydrogel and a silicone based hydrogel, and three drugs with different sizes and charges: chlorhexidine, levofloxacin and diclofenac. Equilibrium partition coefficients were determined at different ionic strength and pH, using water (pH 5.6) and PBS (pH 7.4). The measured partition coefficients were related with the polymer volume fraction in the hydrogel, through the introduction of an enhancement factor following the approach developed by the group of C. J. Radke (Kotsmar et al., 2012; Liu et al., 2013). This factor may be decomposed in the product of three other factors E_{HS},E_{el} and E_{ad} which account for, respectively, hard-sphere size exclusion, electrostatic interactions, and specific solute adsorption. While E_{HS} and E_{el} are close to 1, $E_{ad} >> 1$ in all cases suggesting strong specific interactions between the drugs and the hydrogels. Adsorption was maximal for chlorhexidine on the silicone based hydrogel, in water, due to strong hydrogen bonding. The effective diffusion coefficients, D_e, were determined from the drug release profiles. Estimations of diffusion coefficients of the non-adsorbed solutes $D = D_e \times E_{ad}$ allowed comparison with theories for solute diffusion in the absence of specific interaction with the polymeric membrane.

1. Introduction

The controlled drug release from hydrogels is an important issue for medical applications that has been under intensive investigation in the last decades, both experimentally (Hoare and Kohane, 2008; Ratner and Hoffman, 1976) or through mathematical modelling (Peppas and Khare, 1993; Siepmann and Siepmann, 2008), including empirical/semi-empirical models, as well as mechanistic realistic ones (Caccavo et al., 2015a, 2015b; Kaunisto et al., 2010; Lamberti et al., 2011). Understanding the mechanisms of drug release for each particular pair drug/hydrogel membrane is very important for the optimization of the release kinetics from the delivery devices and also for the construction of good mathematical models which allow correct predictions of the release profiles. The simplest mechanistic model is based on the assumption of a mass transfer process controlled by drug diffusion. However, in many cases, the drug transport through polymeric membranes depends on polymer swelling and drug-polymer interactions, and it should be considered as a diffusional transport process and as a partition phenomenon. Thus, an important feature of the delivery system is the equilibrium partition coefficient, K, of the drug which depends on the relative strength of the interactions of the drug with both the hydrogel and the solvent. It is defined as the ratio between C_{gel} and C_{sol} which are, respectively, the equilibrium drug concentrations in the hydrogel and in the aqueous solution at the end of the drug loading step. The partition coefficient may be

* Corresponding author.
E-mail address: b.saramago@tecnico.ulisboa.pt (B. Saramago).

http://dx.doi.org/10.1016/j.ijpharm.2016.10.047
0378-5173/

related to the polymer volume fraction in the hydrogel, φ, through the introduction of an enhancement factor, E, as follows (Kotsmar et al., 2012):

$$K = E(1-\varphi). \quad (1)$$

Following the reasoning of Dursch et al. (2014), this enhancement factor for a solute in a dilute solution may be decomposed as the product of three individual enhancement factors E_{HS}, E_{el} and E_{ad}. E_{HS} accounts for the hard-sphere size exclusion, E_{el} refers to electrostatic interaction and E_{ad} considers specific solute adsorption on polymer fibers. The hard-sphere solute enhancement factor was calculated by Kotsmar et al. (2012), based on the theoretical mesh size distribution of Ogston for a random assembly of infinitely long fibers, to be:

$$E_{HS} = \exp\{-4\phi[(r_s/r_f)(1+r_s/r_f)]\} \quad (2)$$

where r_s is the hydrodynamic radius of the solute and r_f is the radius of the polymer fiber. $E_{HS} < 1$ reflects partial rejection due to size exclusion, while $E = 0$ indicates that the solute is too large to penetrate the hydrogel network. The electrostatic enhancement factor was introduced by Dursch et al. (2014), based on the Donnan theory (Overbeek, 1969), as:

$$E_{el} = \exp\left(-\frac{ZF\psi}{RT}\right) \quad (3)$$

where Z is the charge number of the solute, F is the Faraday constant, ψ is the Donnan electric potential difference between the hydrogel and the bulk aqueous solution, R is the gas constant and T is the temperature. For nonionic solutes $E_{el} = 1$, while $E_{el} > 1$ indicates electrostatic attractions between the solute and the polymer and $E_{el} < 1$ reflects electrostatic repulsions.

The specific solute adsorption enhancement factor, E_{ad}, may be calculated, assuming that the solutes are dilute, by:

$$E_{ad} = \left[1 + K^H\varphi/(1-\varphi)\right] \quad (4)$$

where K^H is Henry's constant for solute adsorption on the polymer chains (Kotsmar et al., 2012).

At dilute concentration, solute diffusion in a nonadsorbing gel follows Fick's second law with a constant diffusion coefficient, D. This law may be extended to account for the solute specifically adsorbed to the polymer which is different from that diffusing in the liquid-filled spaces (Liu et al., 2013). The resulting equation involves the number of moles of non-adsorbed solute in the liquid-filled voids per liquid volume, C, and the number of moles of specifically adsorbed solute per unit polymer volume in the gel, n:

$$\frac{\partial C(t,x)}{\partial t} + \left(\frac{\varphi}{1-\varphi}\right)\left(\frac{\partial n(t,x)}{\partial t}\right) = D\left(\frac{\partial^2 C(t,x)}{\partial x^2}\right). \quad (5)$$

This equation is valid under the following assumptions: (1) hydrogel swelling is not affected by the presence of the solute in dilute conditions; (2) diffusion occurs within the liquid phase of the hydrogel; (3) surface diffusion along the polymer chains is negligible. If n is given by Henry's law $n = K^H C$, an effective diffusion coefficient, D_e, describing solute transport in the gel may be defined (Liu et al., 2013):

$$De = D/1 + K^H\varphi/(1-\varphi) \quad (6)$$

Eq. (6) together with Eq. (4) yields:

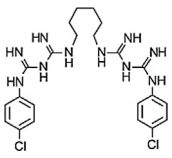
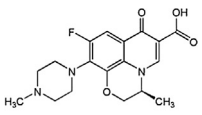
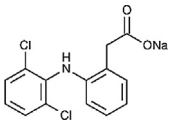
$$D = D_e E_{ad} \quad (7)$$

As $E_{ad} > 1$, $D > D_e$, which means that the drug diffusion inside the hydrogel is retarded by drug adsorption on the polymer chains.

In the present work, an investigation of the loading and release process of ophthalmic drugs in hydrogels used as contact lens materials was presented. The partition and diffusion coefficients were determined and the interpretation of the obtained results at the light of the existing theories was attempted. Three drugs, namely chlorhexidine (CHX), levofloxacin (LVF) and diclofenac (DIC), and two hydrogels which were recently investigated by our group (Paradiso et al., 2014a,b): a poly-hydroxyethylmethacrylate (pHEMA) based hydrogel and a silicone based hydrogel, were considered for this study. Chlorhexidine is used as antibacterial agent and topical disinfectant (Mathers, 2006), levofloxacin is an antibiotic that is widely used both in the prophylaxis and treatment of ocular infections (Dajcs et al., 2004), and diclofenac is a nonsteroidal, anti-inflammatory drug with analgesic activity (Goa and Chrisp, 1992). The characteristics of the drugs are given in Table 1.

The hydrodynamic radii (r_s) of the solutes were determined from measurements of the bulk aqueous diffusion coefficients, D_0,

Table 1
Chlorhexidine, levofloxacin and diclofenac characteristics.

Drug	Structure	Ionicity	Solubiliy in water at 20 °C (mg/mL)	MW (g/mol)	pKa
CHX		Cationic	19	643.57	10.52
LVF		Zwitterionic	25	361.37	6.24 8.74
DIC		Anionic	2.37	318.13	4.15