International Journal of Pharmaceutics 532 (2017) 502–510

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Research Paper

Modeling drug release through stimuli responsive polymer hydrogels

Aditya Pareek, Shantanu Maheshwari, Sivakumar Cherlo, Rama Subba Reddy Thavva, Venkataramana Runkana*

TCS Research, Tata Consultancy Services Ltd., Tata Research Development and Design Centre, 54-B, Hadapsar Industrial Estate, Pune 411013, India

ARTICLE INFO

Keywords:
Polymer hydrogels
Controlled drug delivery
Mathematical modeling
Deformation
Release kinetics
pH sensitive

ABSTRACT

There is a rising interest in stimuli-responsive hydrogels to achieve controlled and self-regulated drug delivery. Stimuli responsive polymer hydrogels with their ability to swell/de-swell under varying pH conditions present themselves as a potential candidate for controlled drug delivery. It is important to develop a mechanistic understanding of the underlying phenomena that will help suggest ways to control the drug release from a polymer hydrogel. We present a mathematical model that couples Nernst–Planck, Poisson and force balance equations to incorporate diffusion of ionic species and drug along with deformation of hydrogel under osmotic pressure. The model can be used to simulate swelling behaviour of the hydrogel along with the kinetics of drug release. It has been validated with published experimental data for swelling of polyhydroxyethyl methacrylate-*co*-methacrylic acid (pHEMA-*co*-MA) gels and release kinetics of Phenylpropanolamine from these gels. Effect of formulation parameters such as polymer concentration and cross-linker concentration has also been evaluated. The model can be used to reduce the number of exploratory experiments required during design of a drug delivery system.

1. Introduction

Limited drug efficacy, undesirable temporal changes in drug concentration and patient non-compliance due to frequent dosing schedule have given impetus to the design of controlled drug delivery systems (Uhrich et al., 1999). Polymer micro/nano-particles have been developed to deliver the encapsulated therapeutic molecules over a prolonged period of time using subcutaneous, intravenous and pulmonary routes (Almeida and Grenha, 2014; Gref et al., 2012; Mann and Raskin, 2014). However, oral drug delivery due to its convenience has been considered to be the most preferred route (Rekha and Sharma 2013; Shaji and Patole, 2008). The challenge lies in protecting the therapeutics from highly acidic conditions prevailing in the gastro-intestinal (GI) tract (Evans et al., 1988). Several therapeutic molecules especially proteins degrade due to acidic pH encountered while passing through the GI tract (Bruno et al., 2013). Polymer hydrogels due to their biocompatibility and swelling controlled release have emerged as potential vehicles of drug molecules (Bawa and Pillay, 2009; Hoare and Kohane, 2008). In particular, pH sensitive polymer hydrogels with their desirable swelling property have been recognized as a potential carrier for oral delivery of such therapeutic drugs (Chaturvedi et al., 2013; Hoffman, 2012). These hydrogels can minimize drug release under acidic conditions and allow its egress under neutral/basic pH. Oral drug delivery systems based on pH sensitive hydrogels have been synthesized on the laboratory scale (Dalmoro et al., 2010; Hu et al., 2015; Yang et al., 2013). These hydrogels differ in terms of polymer composition and consists of monomers which contain ionisable groups such as amine or carboxylic acid. These groups remain fixed in the polymer network as the hydrogel forms an insoluble structure due to crosslinking (Langer and Peppas, 2003). The fixed charged groups which are in the form of weakly basic groups (in case of cationic hydrogels) or weakly acidic groups (in case of anionic hydrogels) undergo ionization at suitable pH that eventually leads to the swelling of gels (Peppas et al., 2000).

Development of oral drug delivery systems based on pH sensitive hydrogels to deliver therapeutics is an active field of research (Wang et al., 2010; Gao et al., 2012; Koetting and Peppas, 2014; Watkins and Chen, 2015). The development of a polymer hydrogel based drug delivery vehicle is a design problem. For a particular drug, one needs to select the polymer and its concentration, solvent, cross-linking agent and its concentration, along with the synthesis procedure to arrive at a particular size and shape of the delivery vehicle (Park et al., 2010). However, the experimentation based design can be time and resource consuming. Mathematical models that incorporate the underlying phenomena of drug release from delivery systems can significantly reduce the number of experiments (Grassi and Grassi, 2014; Lamberti, 2015; Peppas and Narasimhan, 2014; Rothstein and Little, 2011).

Mathematical models have previously been used to explain the factors involved and predict swelling behaviour and drug release from

* Corresponding author.
E-mail addresses: venkat.runkana@tcs.com, venkat.runkana@gmail.com (V. Runkana).

http://dx.doi.org/10.1016/j.ijpharm.2017.09.001
Received 13 April 2017; Received in revised form 31 August 2017; Accepted 1 September 2017
Available online 05 September 2017
0378-5173/

Nomenclature

c_i	Concentration of species [mol/m^3], $i \in \{1,2,3,4\}$
c^s_{m0}	Initial concentration of fixed charged groups in hydrogel [mol/m^3]
D_i	Diffusion of species i in water [mol/m^3], $i \in \{1,2,3,4\}$
$\overline{D_i}$	Diffusion coefficient of species i in gel [mol/m^3], $i \in \{1,2,3,4\}$
E_Y	Elastic modulus of gel [Pa]
E	Green-Lagrange strain [—]
F	Faraday's constant [C/mol]
F_A	Force per unit area [Pa]
F_D	Deformation gradient tensor [—]
F_v	Force per unit volume [N/m^3]
H	Hydration state of the hydrogel
K_a	Dissociation constant of fixed charged group, [mol/m^3]
N	Unit normal to a boundary [—]
$P_{osmotic}$	Osmotic pressure [Pa]
S	Second Piola-Kirchhoff stress tensor [Pa]
T_0	Temperature of the system [K]
R_{bulk}	Radius of the computation domain [m]
u_x	Element of deformation vector in the x-direction [m]
u_y	Element of deformation vector in the y-direction [m]

Greek symbols

ψ	Electric potential [V]
μ_i	Mobility of the ionic species i [s.mol/kg], $i \in \{1,2,3\}$
ρ_v	Charge density inside the gel [C/m^3]
	Density of hydrogel at dry state [kg/m^3]
ρ_w	Density of water [kg/m^3]
ν	Poisson ratio of the gel [—]
$\in_x$	Strain in the x-direction [—]
$\in_y$	Strain in the y-direction [—]
λ	First Lamé parameter [Pa]
μ	Second Lamé parameter [Pa]
ε	Relative permittivity of water [—]
ε_0	Permittivity of vacuum [F/m]
ϕ	Polymer volume fraction [—]

hydrogels. Neutral hydrogels such as hydropropyl methylcellulose (HPMC) have been modelled by accounting for diffusional mass transport of drug molecules and water along with first-order dissolution kinetics of the gel to explain drug release kinetics observed in the experimental studies (Siepmann et al., 1999; Siepmann and Peppas, 2000). A model to predict drug release from poly-disperse cross-linked polymer hydrogels was developed that included the phenomena of drug dissolution and re-crystallisation as it comes in contact with water (Grassi et al., 2000). Recently, the assumptions of nominal polymer erosion and dilute systems have been relaxed by incorporating a constant erosion rate and Maxwell's law of multi-component diffusion, respectively. Furthermore, flux balances of components namely, water, drug and polymer, at the swelling front have been used to estimate the swelling velocity (Caccavo et al., 2015a,b). Models combining mass transport of solvent and Helmholtz free energy based calculations for deformation of hydrogel have also been proposed to describe and explain the results of stress relaxation tests performed on hydrogels (Caccavo and Lamberti, 2017; Caccavo et al., 2017). Neutral hydrogels swell due to change in chemical potential brought about by mixing of the polymer with water. On the other hand, pH sensitive gels are ionic in nature and swell due to the ionization of end groups present in the polymer chain and the subsequent diffusion of ionic species from the surrounding medium that develops a net driving force for swelling (Peppas et al., 2006; Qu et al., 1999). Therefore, models for predicting the swelling behaviour of hydrogels need to account for electrostatic interaction between the hydrogel matrix and the surrounding medium because the electrostatic interactions influence the transport of ionic species and the forces acting on the hydrogel structure. Mathematical models proposed in the literature so far have mostly focussed on simulation of swelling characteristics of pH sensitive hydrogels only. The earlier models to study hydrogel deformation were empirical in nature that utilized experimental data for hydrogel swelling (Kim et al., 2003). A steady state model to describe hydrogel swelling at different pH was also reported (De et al., 2002). Diffusion of ionic species and hydrogel deformation under osmotic pressure was coupled in this model to estimate the equilibrium swelling of hydrogel. Later models included transport equations for other mobile ions and estimated the concentration profiles of ionic species (Na^+, Cl^- and H^+) inside the hydrogels at steady state (Li et al., 2005; Wallmersperger et al., 2011). Additionally, models for polyelectrolyte gels that include free energy contribution due to deformation of the network, mixing of polymer with solvent and mobile ions, and polarization of the gel have been used to estimate the equilibrium swelling ratio (Hong et al., 2010; Marcombe et al., 2010). Further, free energy formulation of the phenomena along with the Gent model to account for non-Gaussian movement of chains under high swelling ratios was used to study the effect of salinity of the solution and cross-link density on equilibrium swelling behaviour of hydrogel (Li et al., 2014). Mathematical models to study the transient behaviour of ionic hydrogels have not been actively studied. One such model was proposed to predict transient deformation of ionic-strength responsive Poly (acrylamide-sodium acrylate) gels (Achilleos et al., 2000). A model to predict the swelling kinetics of a pH sensitive hydrogel, (pHEMA-*co*-MA), was proposed to estimate change in its diameter when micron sized gel stored at pH = 3 was exposed to a buffer solution at pH = 6 (De and Aluru et al., 2004). The simplification of one-dimensional geometry was relaxed later and the equations were solved for a two-dimensional geometry to predict swelling kinetics of pH sensitive hydrogels (Suthar et al., 2010).

It is necessary to couple phenomena related to swelling as well as drug release in order to predict drug release kinetics from stimuli sensitive hydrogels. For example, Grassi (1999) solved the mass balance equation for solvent (water) to capture swelling phenomena while including the contributions of both Fickian and non-Fickian (due to relaxation time of polymer) behaviour in the total flux calculations. This along with the diffusion equation for the drug was solved in the moving geometry to predict release kinetics of the drug (hydrocortisone) at different temperatures. Podual et al. (2004) adopted a somewhat different approach for glucose-sensitive gels using a linear-kernel for mechano-chemical compliance derived from kinetics of swelling for prediction of volume fraction of water in the hydrogel. Diffusion equations for both solid and dissolved form of the drug were solved to estimate release kinetics as volume fraction of water present in the hydrogel changes as the gel swells. While temperature and glucose are important stimuli for hydrogels, pH is one of the most commonly applied stimuli for oral drug delivery and is the focus of current work.

To accurately capture swelling and drug release kinetics of a pH sensitive hydrogel, we present a mathematical model that incorporates Nernst–Planck equation to account for diffusion of ionic species present in the release medium, Poisson equation to predict the spatial distribution of electric potential, and a force balance equation to estimate the deformation of hydrogel due to the osmotic pressure generated. The above set of equations along with Fick's law of diffusion was used for describing the transport of drug molecules through the hydrogel. This set of coupled equations was solved using the arbitrary Lagrangian-Eulerian (ALE) framework to predict both swelling behaviour of the hydrogel and the drug release kinetics. The model was validated with