Mathematical modelling of controlled release from implanted drug-impregnated monoliths

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Specialized implantable capsule and drug combinations can deliver pre-specified and reproducible drug dosages over a wide spectrum of conditions and durations of therapeutic treatment. Mathematical and computational models of controlled release may provide a reliable design tool for the fabrication of such devices, and may also facilitate the determination of suitable dosages for other drugs of differing chemical and molecular properties without the need for time-consuming animal laboratory testing for each new bioactive agent. The author reviews the evolution of mathematical models for the diffusional release of a solute from both non-erodible and biodegradable multi-layered slab matrices in which the initial drug loading c_0 is greater than the solubility limit c_s.

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▼ Interest in the development of implantable polymeric drug delivery systems capable of modulating drug release as a function of specific time-varying therapeutic requirements dates back to the 1980s. There is currently a new generation of potent drugs emerging as a result of recent advances in biotechnology. These therapeutic drugs and hormones must be administered to the body in a precisely controlled manner[1–4] in order to optimize medical benefits, often by mirroring the physiological release profiles of their endogenous counterparts, which may be discontinuous in nature. Furthermore, many such drugs have a short biological half-life or may be degraded by passage through the gastrointestinal tract, thus precluding oral administration.

Parental drug administration[5] employing chronopharmacological approaches (chronotherapy) has underlined the importance of designing appropriate release kinetics into the implantable device from the outset. Examples of candidates for such intermittent drug delivery include:

- insulin as a means of normalizing glucose levels over a relatively narrow range[6,7];
- parathyroid hormone to accelerate bone healing and remodeling[8,9].

It is important to distinguish between depot formulations, leading to sustained release, and true controlled-release drug delivery, which is the focus of this review. For depot formulations, drug delivery may, for example, be solubility-controlled by insoluble salts, oil emulsions or other approaches[10]. Alternatively, one may consider dissolution-controlled drug delivery in which a phase erosion of the polymer carrier is associated with fast or slow dissolution of the macromolecular chains[11]. Diverse strategies in controlled drug delivery were reviewed recently[12].

Controlled-release drug delivery systems

True controlled-release drug delivery systems may be divided into two principal categories:

- delivery systems capable of feedback control [for examples and reviews, see Refs 4, 13–15 and Steward (1995) *Permeability of Polymer Latex Films*, Nottingham Trent University PhD Thesis, Nottingham, UK];
- delivery systems for which the release rate over time is pre-programmed into the device.

This review focuses on the latter category and includes discussion of some relevant mathematical models describing Fickian and non-Fickian

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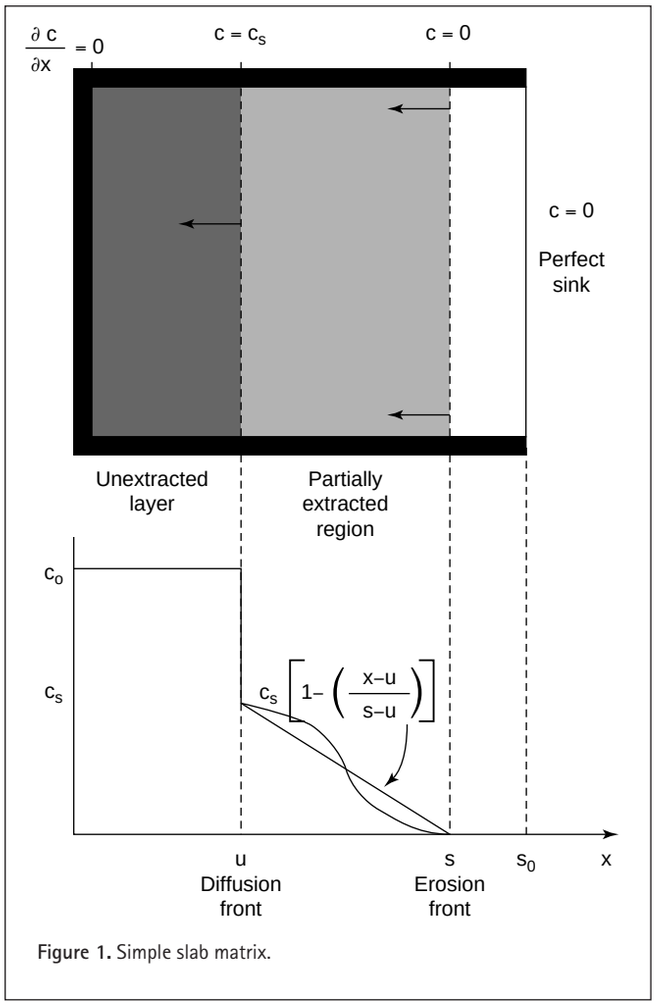

Figure 1. Simple slab matrix.

diffusion as related to drug delivery systems. Only monolithic (matrix) devices are considered here, because these are possibly the most common of the devices for controlling the release of drugs.

Monolithic devices are relatively easy to fabricate, when compared to reservoir devices, and there is less risk of an accidental high dosage, which could result from the rupture of the membrane of a reservoir device. The drug-impregnated matrix is typically formed by compression of a polymer and drug mixture or by dissolution or melting of the mixture followed by solidification. The drug dispersed within the implanted monolithic matrix dissolves and is leached out into the surrounding body tissues. The rates of release, in accordance with Fick's laws of diffusion[16], will depend upon a complex set of physicochemical parameters (Box 1), and certain parameters will dominate depending upon conditions and/or applications (for examples, see Refs 17 and 18).

Box 1. Some factors affecting rates of release from a monolithic matrix

Drug and matrix diffusion coefficients
Drug molecular weight and size
Matrix pore size
Tortuosity of interconnecting channels within matrix
Matrix swelling
Osmotic pressure gradients
Ionic exchanges
Local electromagnetic force fields
Matrix erosion and drug solubility

Mathematical modelling of drug release

The problem can be considered using the simplest possible representation[19] of the moving boundary problem for the diffusion of active component from a one-dimensional slab matrix (Fig. 1). The outer surface of the matrix is considered to erode and to move inward at the same time as a diffusion front, which starts at the exposed surface of the matrix, also moves inward towards the interior of the slab of initial thickness s_0. The scheme can be explained as follows:

- the model adopts the general premise that the drug concentration immediately behind the inward-moving diffusion front is fixed at the solubility limit c_s;
- drug concentration is denoted c(x,t) within the matrix;
- the thickness of the eroding slab at time t is denoted $x = s(t)$;
- the position of the diffusion front is denoted $x = u(t)$;
- the initial uniform drug loading concentration within the matrix is denoted $c = c_0$.

Both linearized[20] and exact concentration distributions are shown in Fig. 1 for illustrative purposes only.

Governing equations

The distribution of drug concentration c(x,t) within the matrix at any time t and position x is governed by Fick's second law[21]:

$$\frac{\partial c}{\partial t} = \mathrm{div}(\mathbf{D}\,\mathrm{grad}\,c) = \frac{\partial}{\partial x}\left(D_x \frac{\partial c}{\partial x}\right) + \frac{\partial}{\partial y}\left(D_y \frac{\partial c}{\partial y}\right) + \frac{\partial}{\partial z}\left(D_z \frac{\partial c}{\partial z}\right) \quad (1)$$

where the flux is **D**grad c from Fick's first law and **D** is the diffusion coefficient for the drug contained within the pores of the matrix. In general, the matrix may be anisotropic and **D** will depend upon position within the matrix and on time, due to possible spatial and temporal variations, respectively, in

porosity, solubility, etc. In some instances, the diffusion coefficient **D** may also be concentration-dependent.

Fickian diffusion

Diffusional release of the drug is normally governed by Fick's first and second laws. Higuchi[20] first investigated the release of drug from a planar surface and from a spherical pellet, assuming a perfect sink condition ($c = 0$) at the exposed surface of the monolith.

The embedded drug is dissolved and is leached out by the penetrating solvent, diffusing outward through the network of capillary channels filled with the extracting solvent (Fig. 1). A pseudo-stationary state was assumed, implying that the inward progressing diffusion front separating the unextracted region ahead of it from the partially extracted region behind it, moves slowly enough that a linear concentration distribution is obtained between the diffusion front and the exposed surface of the device. Fick's first law is applied across this diffusion front, and this serves to determine the velocity and subsequently the position of the front as a function of time. However, this pseudo-stationary approximation is only appropriate when the concentration c_o of drug initially impregnated in the matrix is much greater than its solubility limit c_s in the matrix (high drug loading). The drug concentration is assumed to fall to its solubility limit immediately behind the inward progressing diffusion front, and a perfect sink condition is maintained at the surface of the matrix. No surface or volume erosion of the matrix was considered by Higuchi[20].

Analytical solutions are possible for some simple one-dimensional or quasi one-dimensional geometries with spatially uniform diffusion coefficients. The linearized concentration distributions are only approximations of the true error function-type distributions resulting from exact solutions of Fick's second law, which governs the passive diffusion process. The pseudo-stationary restriction was subsequently removed by Paul and McSpadden[21] by use of the exact solution for a semi-infinite slab.

The full problem of the Stefan moving-boundary type was considered by Crank[22] and has been discussed in considerable detail by Rubenstein[23]. Lee[24] has approximated the solution of Paul and McSpadden[21], in which transcendental expressions appear, and has generalized it to include erodible matrices by employing the refined version of the heat balance integral method due to Volkov and Li-Orlov[25]. The unsteady Fick's second law (Equation 1) is integrated twice with respect to the spatial coordinate and the concentration distribution in the partially extracted region is approximated by a polynomial in the spatial coordinate. Lee[24] uses a simple quadratic concentration profile that satisfies the boundary conditions to approximate the transcendental expressions of the exact solution on an integral average basis. He finds the integral solutions to be much more accurate than the pseudo-stationary results and much easier to use than the exact solutions. The results are found to be particularly useful for the release of dispersed solute when the solute (drug) loading is not much in excess of the drug solubility in the matrix.

Similarity solution

Marshall and Windle[26] developed a similarity solution for the case of constant c_0 and c_s with a perfect sink condition at the exposed surface. They then perturbed that solution to account for the presence of a thin diffusion boundary layer just outside the exposed surface. The authors also investigated the theoretical possibility of constructing a drug delivery device with a drug release rate that is a pre-specified function of time $\psi(t)$; this would be achieved by introducing into the matrix particular controlled spatial variations of solubility $c_s(x)$ and impregnation concentration $c_o(x)$. By accepting certain simplifications, such as abandonment of the unsteady diffusion equation and a linear (pseudo-stationary) approximation of the drug concentration in the partially extracted layer, they were able to propose the outline of a (numerical) solution that would respect the physical requirements that the thickness of the partially extracted layer must not decrease with time and that the concentration there should remain positive.

More recently, some simpler but possibly more practical analytical and computational solutions have been published for the diffusional release of bioactive agents from impregnated monoliths of various geometries. Abdekhodaie and Cheng[27] obtained exact solutions for solute release from planar and spherical matrices into a finite external volume when the initial solute loading exceeds the solubility limit in the matrix. They considered the process to be diffusion-controlled rather than swelling- or dissolution-controlled. Their solutions, which are based upon a combination of variables method exploiting previously established exact solutions for early time positions of the diffusion front, indicate an increase in fractional release with increasing external fluid volume. Furthermore, for a given external volume, fractional release decreases with an increase in initial drug loading. Similar (computational) results were reported by Collins *et al.*[19] for diffusional release from an eroding slab.

The manufacture of such bioerodible implants, as a means of tailoring the drug output at pre-programmable release rates using several layers of surface eroding polymers combined with bulk eroding polymers, has been reported recently[28]. Göpferich and Langer[29,30] earlier developed theoretical models to predict the erosion rates of two- and three-dimensional surface eroding polymers [such as p(CPP-SA) 20:80, polyanhydrides and poly(D,L-lactic acid)] destined for the local treatment of infections, cancer or vaccine administration. An experimental study of the enhanced diffusional release of drug resulting from

matrix degradation was reported in 1995, supported by a quasi-empirical mathematical model[31]. This model is based on the fact that when the matrix degrades significantly, many channels and crevices are opened throughout the matrix, accelerating drug release. This causes the effective diffusion coefficient to vary over time. Approximate expressions for cumulative mass release were used for the early and late stages of release, respectively: $M_t/M_\infty < 0.4$ and $M_t/M_\infty > 0.6$.

Comprehensive computational model

A far more comprehensive computational model appears to have been formulated in a two-part series recently published by Wu and Zhou[32,33]. They used a finite-difference analysis and took into account complex geometries and composite matrix structures as a means of assessing the factors influencing release kinetics. The model was used to analyse drug release into a finite volume from matrix devices of complex geometries, including a convex tablet, a hollow cylinder, a doughnut-shaped ring and an inward-release hemisphere. Effects of composite structures on release kinetics were investigated for composite pessaries, coated elastomer rings and multi-layered tablets in the first part. In the second of the two-part series, the influences of initial drug concentration distribution, matrix anisotropy and time- and concentration-dependent diffusion coefficients were assessed, as well as the importance of edge- and end-effects in comparison with simpler one- and two-dimensional models, for various coating materials of different permeabilities, as a potential aid in the design of complex drug-impregnated matrix systems. However, the authors recognize that these models neglect the important physical and biological effects of drug absorption from biological membranes, time-varying drug solubility and drug release accompanied by considerable matrix swelling and/or erosion.

The Fickian (also termed Case I) solution is very much complicated by the fact that the position of the moving (diffusion) boundary is not known, except in the course of solving the original problem.

Non-Fickian diffusion

A second type of limiting behaviour – Case II diffusion – was recognized in 1966[34]. It is observed in polymer penetrant systems in which substantial swelling occurs, accompanied by the formation of a sharp diffusion front. Such systems are also used in controlled-release drug delivery devices. Andersson and colleagues have recently pointed out the importance in many gel applications of swelling and shrinking of the polymer matrix, citing examples in controlled and slow release kinetics, which determine the rate of diffusion of active component out of the matrix[35]. Further applications include gel extraction, in which the gel may be swollen and shrunk several times. For typical gels such as poly(*N*-isopropylacrylamide), the pressure vs equilibrium volume curve is bell-shaped, similar to that known for a classic van der Waals gas. The isobars for a gel near a critical point are very reminiscent of the isotherms for a van der Waals gas near its critical point.

Collective diffusion equation

The motion of the polymer network of a gel during the course of swelling and shrinking is governed by a diffusion equation, called the collective diffusion equation. The diffusion coefficient is defined as the ratio of the osmotic bulk modulus, K, of the polymeric network to the frictional coefficient, f, between the polymer network and the liquid, such that $D = K/f$. The displacement vector u (r,t), representing the displacement of a physical point or position within the polymeric network from its final equilibrium position after the gel is fully swollen, is seen to obey the diffusion equation.

The swelling force causing this motion was recently measured as a function of time for the interpolymer complexes formed by graft polymerization of poly(ethylene glycol) (PEG) monomethacylate on poly(methacrylic acid) in various pH-buffered solutions[36]. It was reported that the forces exerted decreased with increasing molecular weight of the PEG graft. The authors found that the swelling force was generally controlled by the relaxation process of the macromolecular chains, causing a significant deviation from pure (Case I) Fickian swelling behaviour.

Characterization of Case II diffusion

Case II (or anomalous) diffusion has been characterized by Fu and Durning[37] as developing:

- a step-like jump in concentration at the sharp boundary, separating a highly swollen (rubbery state) region from a dry, typically glassy region;
- propagation of this sharp front into the polymer at constant velocity, leading to a linear increase in absorbed fluid with time;
- a small Fickian (Case I) diffusion of fluid into the glassy region ahead of the advancing boundary;
- an initial induction time for the establishment of the sharp front.

One-dimensional model for coupled swelling diffusion

Astarita and Joshi formulated an interesting and relatively straightforward one-dimensional mathematical model for the coupled swelling diffusion process of a polymer sample[38]. Solvent at the exposed surface of the polymer is maintained at a constant concentration and infuses into the matrix, causing it to swell. A front, separating the swollen from the glassy region

of the polymer, progresses into the depth of the matrix. Both finite and semi-infinite slabs are considered through variants of the distal boundary condition. The authors were particularly interested in analytical asymptotic solutions in the region of time equals zero. They noted that the sorption of solvents into polymers depends upon the thickness of the polymer in the direction of diffusion.

In most work on swelling in polymers, a nonlinear diffusion coefficient is fitted to the observed behaviour by forcing an awkward dependence of diffusion coefficient on concentration and/or other parameters. They pointed out a fallacy in this approach – that is, as for any functional dependence of diffusion coefficient on other variables, the Boltzmann theorem shows that there always exists a region in the neighbourhood of time $t \cong 0$, in which cumulative mass transfer into the polymer and the distance travelled by any concentration front vary as $t^{1/2}$. They contend that models with variable diffusion coefficient will always predict that the weight sorbed and the distance travelled by the swollen-glassy interface increase linearly with time, while they are observed experimentally, at least at short times, to increase as $t^{1/2}$. The authors are able to obtain the $t^{1/2}$ dependence at short times, evolving into a linear dependence on time at larger times, by accounting for the diffusion of solvent into the glassy region ahead of the advancing front. In so doing, they are obliged to formulate a relation for the swelling kinetics in which they make the following considerations:

- the velocity of the swollen-glassy interface is proportional to the difference to the n^{th} power of the solvent concentration, c, and the solubility limit, c^*, in the swollen region, that is $K(c - c^*)^n$;
- there is a constant value of diffusion coefficient, D, in the swollen region; that is, $K(c - c^*)^n$, and a different constant value D', in the glassy region;
- different degrees of swelling are not accounted for.

An additional mass flux term is added to Fick's first law on the swollen region side of the swollen-glassy interface. All such swelling is assumed to take place on the swollen side of the front, with no swelling in the glassy region, even though some solvent may diffuse into the glassy region ahead of the swollen-glassy interface. This additional mass flux is taken as proportional to $(c - c^*)$ and is assumed to be the driving force that regulates the rate of swelling.

The authors obtained an expression for the total mass of solvent sorbed (into both regions) as the sum of two terms proportional respectively to $t^{1/2}$ and to t. The former dominates for time small and the latter for larger times t. They obtained asymptotic solutions for small and very small sample thicknesses, the latter being relevant to membranes. Model predictions appear to agree well with published results in the literature, except possibly for those few cases in which regional variations in the degree of swelling may have been important.

Estimation of exponent 'n'

Without apparent reference to the rigorously developed work of Astarita and Joshi[38], which had been published some nine years earlier, Ritger and Peppas[39,40] put forth some simplified semi-empirical estimates of the exponent n which appears in their proposed simplified expression for cumulative mass release:

$$M_t / M_\infty = kt^n \qquad (2)$$

Their approximations, based on a partial fit to the classical analytical solutions from Crank[22], may only be useful for preliminary design purposes, as they only predict up to the first 60% of the time release. These approximations indicate qualitative differences in diffusion times are to be expected for different geometries of symmetry and for particle size distributions from monodisperse samples. Their work appears to follow, at a far less detailed level, from the earlier results of Astarita and Joshi[38], confirming that Fickian release initially varies as $n = 1/2$ for all geometries and particle sizes.

For Fickian diffusion, the authors fitted the first 60% of the release curve with values of $n = 0.50$ for thin films; $n = 0.45$ for cylindrical samples and $n = 0.43$ for spherical samples. For swellable controlled-release systems with equilibrium swelling ratios not greater than 25% water content by volume, they suggested values of $n = 1.0$ for thin films, $n = 0.89$ for cylindrical samples and $n = 0.85$ for spherical ones. Implicit in these values are the assumptions that the drug concentration varies linearly with depth in the swollen region and that there is no drug diffusion in the glassy region. A simple first-order kinetic relation was assumed for the cumulative mass release from a thin polymer film.

Fu and Durning[37] suggested that this non-Fickian viscoelastic diffusion may result from a coupling between molecular diffusion and the intrinsic time-dependent response of the polymer to the deformation induced by this diffusion of fluid into it. Indeed, Vrentas *et al.*[41] observed that mass transport is Fickian if the ratio of mechanical relaxation time to characteristic inter-diffusion time is either very large or very small. Only when the two are approximately balanced do viscoelastic effects appear.

The problem has been analysed in considerable mathematical detail by Thomas and Windle[42] in 1982 and subsequently by Durning[43] in 1985, Durning and Tabor[44] in 1986 and Fu and Durning[37] in 1993 for the cases of linear (infinitesimal deformations) and nonlinear viscoelastic diffusion. These developments are briefly discussed below.

If one-dimensional mass transport M(t) per unit area within a polymer slab is characterized (Eq. 2 for small time t) by $M = kt^n$, where k and n are constants, then Fickian (Case I) behaviour corresponds to $n = 1/2$, while for non-Fickian (Case II) transport $n = 1$. The values of the exponent 'n' may vary slightly for cylindrical or spherical geometries. Practically all nonlinear sorption experiments (Fu and Durning[37]) fall into the intermediate range $1/2 < n < 1$, so that Case II diffusion may be viewed as a natural limiting case of nonlinear viscoelastic diffusion.

Transport behaviour of organic penetrants

A comprehensive mathematical theory was developed by Thomas and Windle[42] in 1982 to explain the transport behaviour of organic penetrants in glassy polymers in terms of two basic parameters: the thermodynamic diffusion coefficient D and the viscous flow rate of the glassy polymer $1/\eta_o$, where η_o is the viscosity of the unswollen polymer. The analysis has been developed in three stages:

- determination of the thermodynamic relationship between pressure, concentration and activity of the swelling polymer;
- calculation of the swelling kinetics of a sufficiently thin element of matrix, in which Fickian diffusional resistance may be safely neglected, through an estimation of the mechanical viscous resistance of the polymer (gained through creep data) to changes in volume and shape, taking into account that this response may change as the polymer is plasticized by the penetrant solvent;
- characterization of the complete diffusion process resulting from changes in the concentration profile due to creep at constant activity and the change in the activity profile at constant activity-to-concentration ratio in alternate time increments.

Thomas and Windle[42] present their results in the form of total sorption vs time curves and as families of concentration profiles at various times. In this form, they are suitable for direct comparison with experimental measurements. Their one-dimensional formulation for total sorption requires the numerical solution of the coupled field equations governing the fluid concentration, c, and the fluid activity, α, where:

$$\alpha = \exp(\mu_1 - \mu^\circ_1) / RT \qquad (3)$$

and μ^o_1 is the pure liquid potential. The numerical solution, performed using an explicit finite-difference scheme, shows that the viscosity must decrease strongly with concentration for the model to predict Case II behaviour and suggests that the diffusion coefficient D(c) must increase strongly with concentration c.

Analytical asymptotic solutions for diffusion front velocity and induction time

Hui and colleagues[45,46] obtained analytical asymptotic solutions for the diffusion front velocity and the induction time based on the Thomas–Windle[42] model. They took the viscosity $\eta(c)$ to decrease exponentially with concentration c and set the diffusion coefficient D(c) equal to a constant for concentrations $c < c_{crit}$ and equal to infinity for $c > c_{crit}$. Fu and Durning[37] questioned the realism of this prescription of D, while recognizing that it does lead to neat asymptotic steady-state predictions. The latter admitted that the Thomas–Windle model[42] did, nonetheless, capture the essential phenomenological features of Case II diffusion, and they set about improving the accuracy of the numerical methods to evaluate it. They used the method of lines to reduce the governing partial differential equations to a coupled system of ordinary differential equations in time by first partitioning the spatial domain into subintervals, then using finite-difference or finite-element methods to discretize the spatial derivatives. Care must be taken in computing the steep concentration gradients that develop at the travelling wave front. Numerical results from this work confirm the essential features of the foregoing works and indicate that, for thin films, sorption is surface swelling-controlled, whereas for thick films it becomes diffusion-controlled. Their calculations also show that strong nonlinearities in both diffusivity and viscosity are essential for the correct description of Case II transport.

Follow-up on Thomas–Windle-inspired models

Cox and Cohen[47] in 1989 and Edwards and Cohen[48] in 1995 followed up on the Thomas–Windle[41]-inspired models for stress-driven diffusion in polymers and the effects of a changing diffusion coefficient in super-Case II polymer-penetrant systems. As the polymer absorbs fluid in its rubbery state, pressures build up on the solvent within it, and this increases its chemical potential. Cox and Cohen[47] modelled this stress build-up as an amalgamation of the classical Maxwell viscoelastic model and the Kelvin–Voigt elastic model. In their choice of the dependence of the stresses on the solvent concentration itself, and not on the time derivative of that concentration (as attempted previously in 1985 by Durning[43] and which did not result in true Case II behaviour), Cox and Cohen[47] assumed that the medium must be able to support stresses at equilibrium. However, they did not compute the pressure gradients or associated strain or strain-energy fields, but rather left their formulation in terms of internal energy.

The principal purpose here appears to be to contrive a mathematical artifact to supplement the concentration gradient in Fick's second law in order to improve the model description Case II diffusion by, in effect, introducing the 'memory' associated

with nonlinear viscoelastic deformation. Their observations that, in some such systems, the diffusion coefficient significantly increases as the polymer changes from a glassy to a rubbery state would appear to be consistent with the conclusions in 1990 of Siegel and Langer[18]. However, the latter have shown that the very slow (retarded) release of protein drugs from polymers is due more to the mechanism of pore constrictions (narrowed throats between interconnecting pores) than from concentration-dependent diffusion or random pore topology. The junction of capillaries of very different cross-sectional areas, which connect the matrix pores, is predicted by the Siegel-Langer model[18] to lead to arbitrarily high retardations.

It remains to be seen whether further mathematical modelling, coupled with experimental measurements conducted at the matrix pore level, will be successful in quantifying this perceived relationship between the increased solvent pressure induced during polymer swelling and the associated effects on the pore dimensions, and consequently the diffusion coefficients, which are critical in regulating the rate of drug release.

Mechanics-based approach

A very fundamental mechanics-based treatise on the constitutive equations governing the stress-assisted diffusion of solutes in solids was presented by Aifantis[49] in 1980. His treatment of the equations is very rigorous, and includes a number of phenomena of relevance to Case II transport, such as time-dependent plasticity, in which stress and strain are not related one-to-one, and accounts for memory effects by viewing the stress tensor $\underline{\mathcal{T}}$ and diffusive force p, not as functions but as functionals of the corresponding variables. This approach opens the way for formal expressions of the effects of a deformation or temperature history on the diffusion process. However, this interesting possibility is pursued by Aifantis[49] only for an example case in which the diffusion process depends on the history of the basic diffusion variables.

Numerical methods

In general, effective numerical techniques must be devised for computational solutions of these models, although some asymptotic solutions have been obtained in analytical form. Such numerical solutions become all the more necessary as additional complexities associated with other transport mechanisms, such as stress-driven diffusion related to polymer swelling and de-swelling, two- and three-dimensional geometries, erosion and non-isotropic matrix materials etc., are incorporated into the drug delivery models.

Second-order finite-difference algorithms

Hyman *et al.*[50] recently developed second-order finite-difference algorithms for the computational solution of such diffusion problems in strongly heterogeneous and non-isotropic media, and these would appear to be applicable to the case of implantable drug delivery systems. Their approach is based on the support-operators method in which one replaces the classical inner product of vector functions by an inner product weighted by the inverse of the material properties tensor $\underline{\mathcal{D}}$. The flux operator is defined as ($\underline{\mathcal{D}}$ grad) – the material properties tensor $\underline{\mathcal{D}}$ times the gradient, rather than the gradient itself – as one of the basic first-order operators. This results in a conservative finite-difference scheme on logically rectangular grids. The discrete analog of the variable coefficient Laplacian is symmetric and negative definite on nonuniform grids. When the material properties, such as diffusion coefficient D and partition coefficient K, are constant, the discrete flux operator is exact for linear functions. A key to improving the accuracy for non-smooth D is to use the flux operator $\underline{\mathcal{D}}$ grad, rather than the gradient operator grad, as one of the basic first-order operators in Fick's second law.

In these methods, the drug concentrations and the elements of the diffusion coefficient matrix D are defined at the cell centers. Hyman and colleagues[50] point out that when D is discontinuous, the nodal discretization of vector quantities, such as the mass flux (defined by their Cartesian components evaluated at the nodes of the grid), is not as accurate as the surface discretization wherein vector quantities are described by their orthogonal projections into the directions perpendicular to the face of the cells. This is so because the mass flux perpendicular to the cell faces is always continuous, even when D is not.

In this approach, which would appear to be particularly interesting for the higher dimensional geometries of the drug delivery device, the discrete analog of the variable-coefficient Laplacian div $\underline{\mathcal{D}}$ grad can be reduced to two discrete operators: a divergence div, and a flux operator GRAD $\sim -\underline{\mathcal{D}}$ grad, which are the adjoints of each other. This assures a self-adjointed and negative definiteness of the discrete variable-coefficient Laplacian for general computational grids. On rectangular grids in particular, all of the discrete operators reduce to standard finite-difference approximations. The algorithm appears to produce the appropriate harmonic average diffusion coefficient for the mass fluxes when the discontinuous diffusion coefficient is a scalar.

Conclusions

This brief, and consequently incomplete, literature review of mathematical modelling of the release of dispersed solutes from polymeric monolithic matrices spans a 35-year period. It may serve at the same time to draw attention to the mathematical and physical complexities of the subject, particularly for the Case II diffusion processes that occur in swellable polymers, and to point the way towards the organization of measurements on

the pore level for the improvement of the present understanding of the constitutive relations and swelling kinetics, which are critical to a quantitative description of the process. In so doing, many fields of application, aside from the current focus on controlled-release drug delivery, may benefit. Such possible industrial and environmental applications include:

- removal of solvent from polymer solutions during dry spinning[41];
- photoresist technology and microlithography[51];
- diffusional release of pollutants and additives from polymers into the environment[52];
- controlled release of agricultural chemicals[53].

As for the pharmaceutical field of application, it is clear that the development of reliable computational design tools will result in the need for fewer release experiments to bring a particular drug formulation to the market.

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