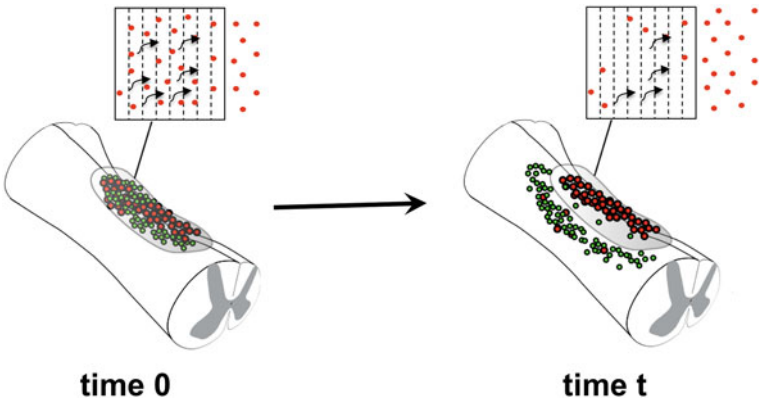
Chapter 2
Principles of Controlled Drug Release: A Mass Transport Matter

In order to exert a therapeutic effect, a drug should have high affinity and selectivity for its intended biological target. For example, a protein or a protein complex in or on a particular cells type should reach a sufficient concentration at that site. In general, to match this goal, the drug has to be released from the delivery system, transported from the site of application to the site of action, biotransformed and finally eliminated through metabolism from the body. In this field the concepts studied in mass transport and in chemical engineering together with polymer science could help to better design and develop suitable scaffolds able to release drugs in a controlled manner.



2.1 Introduction

The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. For example, the traditional drug delivery methods by intravenous injection or by oral ingestion can cause concentration peaks of the drug in the human body. The aim so

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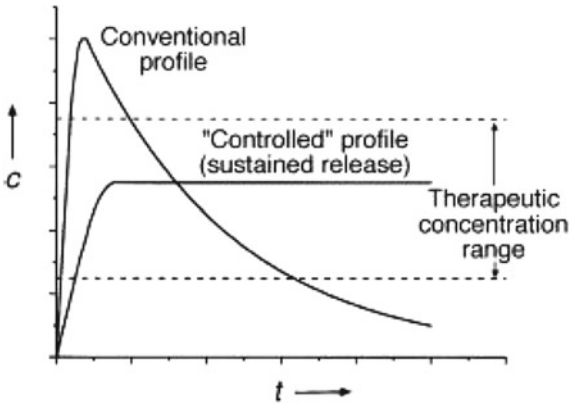


Fig. 2.1 Different drug administration strategies. Reproduced with permission of (Santini et al. 2000)

is to counteract the risks due to under and over dosing maintaining drug level within a desired range (Fig. 2.1).

With classic drug administration to overcome this issue, a multi-dose therapy is necessary. Following this approach we should consider the time where the drug concentration goes below the therapeutic efficacy. Usually the time passed between the assumption of two doses is called *half-life time of the drug* and can be calculated in this way:

$$t_{1/2} = 0.7 \cdot \frac{V_d}{Cl} \tag{2.1}$$

where V_d is the distribution volume of the drug and Cl is the clearance of the system.

In the last years, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. These new strategies, often called smart drug delivery systems (SDDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology. They consist in delivering a certain amount of a therapeutic agent for a prolonged period of time to a target area within the body. Usually drugs are entrapped in carriers that then are implanted or injected into the targeted zone. In Fig. 2.2 are presented the trends of periodic drug administration compared with zero th order release kinetic, where drug concentration is maintained within a desired range for a long period of time.

The adoption of this last strategy presents many advantages:

- Maintenance of haematic concentration within therapeutic values for a prolonged period of time;
- Reduction of side effects;
- Increase of patient's accompliance due to the reduction of the number of administrations.

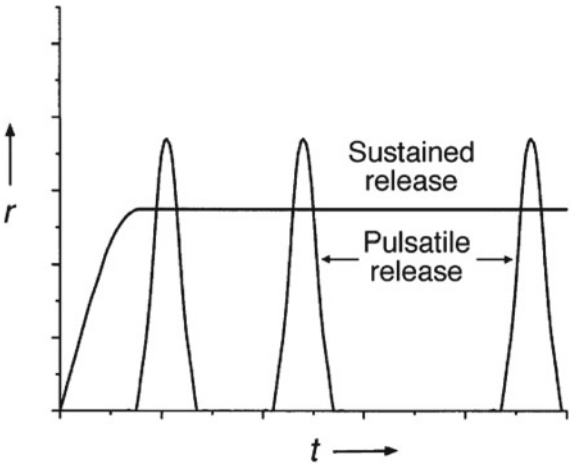


Fig. 2.2 Periodic drug administrations (pulsatile) versus controlled drug release (sustained). Reproduced with permission of (Santini et al. 2000)

2.2 Drug Release Mechanisms

Diffusion controlled systems. Delivery is driven by the gradient of concentration existing between the inside and the outside of the device. The parameter that describes the ability of a drug to diffuse is the diffusion coefficient (D) that depends on many factors like steric hyndrance, temperature, and viscosity. Systems can be of spherical shape, with a bulk of drug surrounded by the polymer (a), or monolithic, where drug is uniformly dispersed into the matrix (b). It is easier to produce monolithic systems, but it is also difficult obtaining zeroth order kinetics because the gradient is not constant (instead of spherical devices), but decreases during time.

Swelling controlled systems. This term can be defined in a strict sense, referring only to devices in which a swelling step is the only release rate-controlling phenomenon. Alternatively, the term "swelling-controlled drug delivery system" can be defined in a broader sense to include devices in which a swelling step is of importance, but also in which other mass transport processes can play a role (e.g. drug dissolution, drug diffusion and polymer dissolution). Often swelling-controlled systems are based on hydrophilic polymers: in dry state (nonswollen state), the polymer network is dense and the mobility of the macromolecules is very much restricted. Upon contact with water, the polymer chains "relax", with two consequences: (1) the mobility of the macromolecules significantly increases and (2) the volume of the system increases. Obviously, the conditions for drug transport in these two states (nonswollen versus swollen) are fundamentally different, and the charge in physical state of the polymer can be used to accurately control the release rate of the incorporated drug.

Bio-erosion controlled system. In this case delivery of drug is promoted by the degradation of the polymeric structure. It is one of the major strategies used in literature and it consists in selective breaking of some chemical bonds present in the polymeric chains up to its reduction to oligomer or monomer that human body is able to eliminate.

Hydrolysis is the most frequent process exploited to break the chains: it occurs when a longer chain (with m + n units) is divided in two shorter chains (with respectively m and n monomeric units) by the addition of a molecule of water:

$$P_{m+n} + W \rightarrow P_n + P_m$$

If the diffusion of the water into the polymer matrix is faster than the de-polymerization kinetics, then an uniform degrade on the entire matrix takes place: this is the case of the bulk degradation (a). Vice versa, when the erosion dynamics is faster than the water diffusion, superficial degradation (b) occurs.

Osmosis controlled systems. The devices employed are called "elementary osmotic pumps" and they are constituted by a central core osmotically active (which contains drug) surrounded by a semi-permeable polymeric membrane with one hole. When the pumps are immersed in watery fluid water goes across the whole (or it diffuse across the polymer) and dissolves the drug then the mixture goes out of the hole again. This device works only if drug is sufficiently water-soluble.

2.3 Diffusion in Polymeric Matrices

As said, diffusion in polymeric systems strongly depends also on the concentration and degree of swelling of polymers. Various techniques, such as membrane permeation, fluorescence and dynamic light scattering, have been used, resulting in a better knowledge on polymer morphology, mass-transfer phenomena and, more recently, the controlled release of drugs from polymeric carriers. "Conventional" model (fickian, non-fickian, mutual diffusion), and physical models based on different concepts (obstruction effects, hydrodynamic interactions, free volume theory) can be found in literature.

2.3.1 Conventional Models

In the study of solvent diffusion in polymers, diffusive process depends on physical properties of polymer network and on solvent/polymer interactions. Alfrey et al. (1966) proposed a functional relation for the amount of solvent absorbed per unit area (M_t) of polymer at time t:

$$M_t = k \cdot t^n \quad \left[1/2 \leq n \leq 1\right] \tag{2.2}$$

where k is a constant and n a parameter related to the diffusion mechanism, considering fickian and non-fickian diffusion as the limiting types of transport processes.

2.3.1.1 Fickian Diffusion

Fickian diffusion is typical of polymeric networks when the temperature is well above the glass transition temperature (T_g). Thus the polymer is in the rubbery state and its chains present a higher mobility that allows an easier penetration of the solvent. A large gradient of solvent penetration is observed in the system due to a solvent diffusion rate (R_{diff}) faster than the polymer relaxation rate (R_{relax}). The detailed Fick's laws were presented in Chap. 1. The solvent concentration profile shows an exponential decrease from the swollen region to the core of the network. Moreover, Fickian diffusion can be also observed in polymer systems below T_g with the addition of a plasticizer.

2.3.1.2 Non-Fickian Diffusion

On the other hand, non-Fickian diffusion is often observed in glassy polymers, i.e. when the temperature is below T_g. In this case chains are not sufficiently mobile to allow immediate penetration of the solvent. There are two categories, depending on the solvent diffusion rate:

$R_{diff} \approx R_{relax} \rightarrow$ the so – called "anomalous diffusion"
$R_{diff} \gg R_{relax} \rightarrow$ for the solvent with a high activity coefficient, characterized by:

(a) Rapid increase of the solvent concentration in the swollen region, which leads to a sharp solvent penetration front;
(b) The solvent concentration is quite constant in the swollen region behind the penetration front;
(c) The solvent penetration front advances at a constant rate, thus the diffusion is directly proportional to time: $M_t = k \cdot t^n$;
(d) There is an induction time of Fickian concentration profile which precedes the solvent penetration front into glassy polymer core.

2.3.1.3 Self-diffusion and Mutual Diffusion

According to Fick's first law, the diffusivity could be defined as the transfer rate of diffusant across diffusion section divided by space gradient concentration at this specific section. Considering the mixing of two pure species, A and B, without volume variation, an equal quantity of each component will be transferred in the opposite direction. From a diffusion point of view, one diffusion coefficient is obtained that is related to both species, referred to as the *mutual diffusion coefficient*.

Moreover it is important to note that the mutual diffusion coefficient, D_m, can be written as the sum of two *intrinsic diffusion coefficients* related to each individual component:

$$D_m = V_a C_a (D_b - D_a) + D_a \tag{2.3}$$

where C_a is the amount of component A contained in the system, V_a the constant volume of component A and D_i the intrinsic diffusion coefficient of component i.

In polymer solutions and gels (already equilibrated systems) there is no volume variation and no mass transfer. Nevertheless, the molecules are in motion and diffusion occurs without the presence of a concentration gradient. In this case the diffusion is defined by the *self-diffusion coefficient*. This diffusion coefficient can be related to the intrinsic diffusion coefficient (thus indirectly related to the mutual diffusion coefficient) by:

$$D_a = D \cdot C_a \cdot \frac{\partial \mu_a}{\partial C_a} = R \cdot T \cdot D \cdot \frac{\partial \mathrm{In} a_a}{\partial \mathrm{In} C_a} \tag{2.4}$$

where D is the self-diffusion coefficient of component A, μ_a the chemical potential and a_a the thermodynamic activity of component A. Self-diffusion takes place in systems that are composed by chemical species in the same phase, such as polymer solutions. When the concentration of the studied species is very small, the self-diffusion of the species is also called *tracer diffusion*.

2.3.2 Theories and Physical Models

2.3.2.1 Obstruction Effects

In the diffusion models based on obstruction effects, polymer chains are regarded as motionless relative to the diffusing molecules represented by solvents and/or solutes. This kind of approximation is based assuming that the polymer self-diffusion coefficient is much smaller than that of the diffusant. Indeed the polymer is here represented as fixed and impenetrable segments immersed in a solution. The presence of the motionless polymer chains leads to an increase in the mean path length of the diffusing molecules between two points in the system.

Maxwell and Fricke (Cheever et al. 1985; Pickup and Blum 1989; Waggoner et al. 1993; Griffiths et al. 1995), studying the dog blood medium, first introduced the following equation:

$$\frac{D(1-\varphi)}{D_0} = \frac{1-\varphi'}{1-\varphi'/\chi} \tag{2.5}$$

where D is the diffusion coefficient, D_0 is the diffusion coefficient in pure solvent, φ is the volume fraction of the polymer, φ' is the volume fraction of the polymer plus non-diffusing solvent bound to the polymer, and χ is a factor depending on the solvent shape (ranging from 1.5 for rods to 2.0 for spheres). Moreover Langdon and Thomas (Thomas and Langdon 1971) found a linear dependence of the self-diffusion coefficient on gel composition for agar hydrogels where electrolyte concentration is low. They suggest that the hindrance to diffusion is due to the hydration of the agar molecules. Their theory, in according to other experimental studies, provides good results for small diffusing particles in dilute polymeric systems. Then, Mackie and Meares (1955) developed the Fricke's concept in order to describe the diffusion of electrolytes in resin membrane, assuming that polymer mobility is less important than mobility of ions or water, so that sites occupied by the polymer are permanently unavailable to ions or water. Thus, motionless polymeric chains impose a tortuosity (or an increase) in path length for small molecules in motion. The diffusion coefficient of a small molecule, equal in size to the monomer segment, is given by the following equation:

$$\frac{D}{D_0} = \left[\frac{1-\varphi}{1+\varphi}\right]^2 \tag{2.6}$$

This model provided satisfactory results over a wide range of concentrations, but correlation between data and theory becomes weaker for large-size diffusant. Authors attributed this divergence to the interactions between larger diffusants and polymer chains. Wang (1954) proposed the following equation to get over this problem:

$$\frac{D}{D_0} = 1 - \alpha\varphi \tag{2.7}$$

where α is a parameter that depends on diffusant geometry. This model is commonly used to describe diffusion in microemulsion systems, but despite the introduction of a geometrical parameter (α), the Mackie-Meares equation presents a better agreement with experimental data. Moreover, Ogston developed an approach for the diffusion of larger diffusants.

He considered the polymer as a cage in three-dimensional networks formed by a random distribution of long chains. Consequently, self-diffusion coefficient for a given diffusant molecule depends both on the size of obstacle present in the solution and on size of the diffusant, as shown by the following equation:

$$\frac{D}{D_0} = \exp\left[-\frac{R_h+\rho}{\rho}\cdot\varphi^{1/2}\right] \tag{2.8}$$

where φ is the volume fraction of the polymer, R_h the hydrodynamic radius of the diffusing molecule and ρ defines the effective cylindrical radius of the fibers. Diffusing molecules are considered as non-perturbing for the network. Therefore, this

model should be applicable to polymeric solutions and gels. Nevertheless, the experimental data showed different results depending on the polymers used. It has been demonstrated that Ogston model remained valid for dilute or semidilute polymeric solutions, but did not provide satisfactory results for large molecules despite the introduction of parameters related to the sizes of both the solute and the polymer. The deviation is indeed more pronounced for concentrated polymeric solutions. In order to improve the approach of Ogston, Johansson developed a new diffusion model for spherical solutes in polymer solutions and gels (Johansson et al. 1991). This theory, called the "hard sphere theory" was based upon four main assumptions:

- steric hindrance causes the reduction of solute diffusion
- hydrodynamic interactions are negligible in the polymer solutions and gels;
- the steric hindrance is caused by the static network, not by the interaction with diffusing species;
- the network structure is decomposed into a set of cylindrical cells and the contribution from each cell to the diffusion coefficient is determined by the distribution of spaces in the network.

In this model, the authors consider the importance of hindrance due to polymer chains that are evaluated as dependent not only on size of the diffusant and amount of polymer but also on properties of polymer chains. Physical properties that they considered are thickness and stiffness.

The mathematical dissertation expressed the diffusion quotient (D/D_0) as the result of local flows in microscopic subsystems. In addition, to quantify the hindrance of polymer chains the authors take into account the closest distance (R) between a point in the network and the fiber. Here the diffusion coefficient is given by following expression:

$$\frac{D}{D_0} = e^{-\alpha} + \alpha^2 e^{\alpha} E_1 \cdot (2\alpha) \tag{2.9}$$

where α is a parameter related to the physical properties of both the polymer and the diffusant:

$$\alpha = \left[\frac{R_h + \rho}{\rho}\right]^2 \cdot \varphi \tag{2.10}$$

where φ is the volume fraction of the network, ρ is the polymer radius and R_h the hydrodynamic radius of the diffusant. In Eq. 2.9 E_1 is an exponential integral:

$$E_1(x) = \int_x^{\infty} \frac{e^{-u}}{u} du \tag{2.11}$$

Despite the complexity of the theory, there are several discrepancies with the data in literature. The model fails for high α values (large-sized diffusants), predicts

Table 2.1 Diffusion model based on obstruction effects

Authors	Applications
Maxwell-Fricke	Solvents and small-sized diffusants
	Very dilute polymer solutions
Mackie and Meares	Solvents and small-sized diffusants
	Semi-dilute polymer solutions
Ogston et al.	Solvents and small-sized diffusants
	Semi-dilute polymer solutions
Hard sphere theory	Solvents and small-sized diffusants
	Semi-dilute polymer solutions

correctly the obstruction due to the polymer, but underestimates the diffusion coefficient at larger R_h. It appears that all the obstruction effect models can fit self-diffusion coefficient data of small molecules in dilute or semi-dilute polymer solutions (Table 2.1).

2.3.2.2 Hydrodynamic Theories

Hydrodynamic theories usually consider the hydrodynamic interactions that are present in the system between solvent and polymer. Indeed these interactions can include frictional ones between:

- the solute and the polymer;
- the solute and the solvent;
- the solvent and the polymer.

In 1984 Cukier (1984) developed an equation that can describe the diffusion of Brownian spheres. In his theory, the semi-dilute solution was considered as a homogeneous monomer unit environment as the polymer coils overlap, in comparison to the dilute solutions where the polymer chains do not interact with each other. Indeed, the whole semi-dilute solution was viewed as a uniform solvent-polymer mixture. The dilute solution was considered as an inhomogeneous system composed of both polymer–solvent and pure solvent domains. This semi-dilute solution of the polymer was approximated as motionless relative to the diffusing solvent, and represented by randomly distributed spheres immersed in an incompressible Navier–Stokes fluid. Thus, the diffusant was considered to undergo screening effects due to the overlapping of the polymer chains, and its diffusion coefficient as follows:

$$D = D_0 \exp(-\kappa R_h) \tag{2.12}$$

where κ represents the screening hydrodynamic interactions between the polymer and the solute in a semi-dilute polymer solution, and R_h is the hydrodynamic radius of the diffusing sphere. In the case of rod-like polymer molecules, the screening parameter was found to have the following relationship:

$$-\kappa_L^2 = \frac{\xi_L n_L}{\eta} \tag{2.13}$$

where ξ_L is the friction coefficient for one rod, n_L the number density of rod-like polymer molecules and η the solution viscosity.

The rod friction coefficient depends on the length and diameter of the rod (L and b, respectively, with $L >> b$):

$$\xi_L = \frac{6\pi\eta(L/2)}{\mathrm{In}(L/b)} \tag{2.14}$$

On the other hand, the dependence of the screening parameter for coil-like polymer molecules can be written as:

$$\kappa_D^2 = \frac{\xi \cdot n_a^*}{\eta} = 6 \cdot \pi \cdot n_a^* \cdot a \tag{2.15}$$

where n_a^* is the monomer number density and a the monomer radius. Limitations of this approach were shown when the model was used for large-sized diffusants such as polymers or proteins, and for the diffusion of linear and star-branched polymers, like polystyrene. The screening parameter, which was found proportional to the polymer concentration, had shown to vary, as noted by Cukier. All the following studies showed that the self-diffusion coefficient of a diffusant in a polymer solution is closely related to the polymer concentration. However, the exponent of the polymer concentration dependence is not a simple constant value and disagreement remains. In parallel with the Cukier's model, Altenberger developed another theory (Altenberger et al. 1986). He considered the rigidity of the body of the polymer as immobilized points randomly distributed in a solution. The solvent is considered as an incompressible Newtonian fluid, filling the space between these points. A small molecule in solvent will interact with these points that represent the network.

Thus, the hydrodynamic interactions were represented by the friction with the stationary points. The mobility of a diffusant will depend on the concentration of the obstacle, i.e. the polymer. At low concentrations (dilute or semi-dilute regimes) the interactions are weak and the diffusion coefficient is given by:

$$D = D_0 \exp(-\alpha \cdot c^{1/2}) \tag{2.16}$$

where α is a parameter that depends on the diffusing particle, and c represents the number concentration of obstacle (the polymer). A more phenomenological approach was used by Phillies (1987; Phillies et al. 1989) to describe the self-diffusion behavior of macromolecules self-diffusion over a wide range of concentrations. The stretched exponential equation was proposed based upon numerous experimental data from his own research, and the polymer self-diffusion coefficient obeys to a scaling law:

$$D = D_0 \exp(-\alpha c^{\nu}) \tag{2.17}$$

where α and ν represent the scaling parameters that depend on the molecular weight of the diffusant polymer. Experimentally, α was found to depend on the diffusant molecular weight ($\alpha \approx M^{0.9\pm0.1}$) for macromolecules, whereas α depends on the diffusant hydrodynamic radius ($\alpha \approx R_h$) for smaller molecules. The scaling parameter ν should scale between 1 for low molecular weight diffusant and 0.5 for high molecular weight diffusant. Between these limits $\nu \approx M^{-1/4}$. Phillies considered three regimes of concentrations defined for reptation theories: i.e. dilute solution where polymer chains move independently, semi-dilute solutions where polymer chains start to overlap, and concentrated solutions where diffusion is dominated by polymer friction. These regimes can be regarded as close to the polymer solutions examined by Cukier, where forces in solution were defined as predominantly hydrodynamic for the last two regimes.

The stretched exponential equation of Phillips is based on following assumptions:

- self-similar effect of infinitesimal concentration increment on D;
- functional form for hydrodynamic interactions between mobile polymer chains;
- dependence of chain extension on polymer concentration.

The first assumption means that an infinitesimal increase of concentration increases drag coefficient of the diffusant. This assumption is based on the fact that polymer self-diffusion coefficient is related to its drag coefficient (f) by the Einstein relation:

$$D = \frac{k_B \cdot T}{f} \tag{2.18}$$

where k_B is the Boltzmann constant and T the temperature. The polymer should retard the diffusant and thus increase the drag. One thing that should be considered is the drag coefficient of the solution, that already retards the diffusant particle. Moreover we should note that polymer-polymer interactions are mainly in hydrodynamic modes rather than in entanglement modes.

Nevertheless, Eq. 2.18 does not consider a screening effect parameter because polymer chains were regarded as mobile, thus no fixed sources of frictional interactions present in the solution. Indeed, polymer chains in solution will reduce both flow rate and molecular diffusion as chains rotate. Another important hydrodynamic model is the reptation theory, which was first introduced by de Gennes (1971), who took into account self-diffusion of a polymer chain of molecular weight *MW* moving inside a three-dimensional network of polymer chains of molecular weight MW-P, which is considered as a hydrogel. Here diffusing polymer chain is considered as constrained by fixed obstacles (gel chains). So the leading motions of polymer chain are feasible only at the extremities and the motion of the central part of the chain should be considered when the extremity enters inside a new tube.

Therefore, only "tubular" motion is conceivable and lateral motion is not considered, as diffusant polymer is enveloped by the network.

Brownian motion for high molecular weight polymers in the tube depends on their molecular weight:

$$D \approx MW^{-2} \tag{2.19}$$

Several years later, de Gennes re-examined reptation theory in order to introduce scaling concepts. He considered also the effect of matrix on self-diffusion coefficient of diffusant. This new model is defined by the following equation (de Gennes 1976, 1979):

$$D \approx MW^{-2}c^{(2-v)\,(1-3v)} \tag{2.20}$$

where MW is the molecular weight of the diffusant, c the polymer matrix concentration and v the Flory exponent for excluded volume.

In semi-dilute regime, this equation leads to two distinct equations:

- $$\text{Good solvents}(v = 3/5) : D \approx MW^{-2}c^{-1.75} \tag{2.21}$$

- $$\theta\,\text{solvents}(\text{v} = 1/2) : D \approx MW^{-2}c^{-3} \tag{2.22}$$

The θ solvent regime corresponds to an exact cancellation between steric repulsion and van der Waals attraction between monomers. The latest model in this field, is the one developed by Gao and Fagerness. In reality, they did not elaborate the model considering hydrodynamic arguments, but the form of their equation is very similar to that of the hydrodynamic theories' equations. Gao and Fagerness (1995) observed exponential decrease of both adinazolam and water diffusion with increasing hydroxypropyl methyl cellulose (HPMC) concentration. Diffusion measurements in HPMC gels were also carried out in the presence of glucose, or lactose, or maltoheptaose (monomer, dimer and oligomer of the HPMC, respectively), which were defined as Viscosity-Inducing-Agent (VIA). A significant decrease in adinazolam self-diffusion coefficient was reported with increasing size of the VIA in the adinazolam–water–VIA ternary solutions.

Their results indicated that drug diffusivity in a multi-component system was influenced by all the components present in the system:

$$D = D_0 \exp(-K_H c_H - K_L c_L - K_A c_A) \tag{2.23}$$

where c_H, c_L and c_A are concentrations of HPMC, lactose and drug (adinazolam), respectively. Good agreement was found between measured and calculated self-diffusion coefficients over a wide range of HPMC concentrations (0–30 wt%).

2.3.2.3 Models Based on the Free Volume Theory

The free volume concept in polymer science is well known: the volume that is not occupied by matter. More generally, free volume can be specified as the volume of a given system at the temperature of study minus the volume of the same system at 0 K. Thus, rearrangement of free volume creates holes that can be used by particles to diffuse. Free volume is contributed by all species present in the system, solvent, solute(s) and polymer. Free volume's theories are based on the assumption that free volume is the major factor controlling diffusion rate of molecules. The first diffusion model based on free volume theory was proposed by Fujita (1961), Masaro and Zhu (1999). The measurements were carried out in a ternary system that includes a solvent, a polymer and a penetrating molecule (a plasticizer). Therefore, the average free volume in such a system was contributed by polymer and solvent. In order to estimate the free volume, Fujita used the concept of Cohen and Turnbull (1959), which defines the probability $P(v^*)$, to find holes of size v^* in a liquid of identical molecules:

$$P(v^*) = A \exp\left(-\frac{bv^*}{f_v}\right) \tag{2.24}$$

where A is constant, b a numerical factor of the order of unity and f_V is the average free volume per molecule. The product bv^* is interpreted as the measure of the minimum hole size required for diffusant displacement B.

This diffusion model is based on these assumptions:

- diffusion process occurs because of redistribution of the free volume within the matrix;
- redistribution of the free volume does not require energy change;
- diffusion process is enabled when the free volume exceeds holes of size v^*;
- diffusion is directly proportional to the probability $P(v^*)$ of finding a hole of volume v^* or larger adjacent to diffusant molecule.

Fujita assumed that Eq. 2.24 was valid also in the case of a binary system. Further, the probability that molecule found in its surrounding a hole large enough to allow displacement is closely linked to diffusant mobility, m_d:

$$m_d = A \exp\left(-\frac{B}{f_v}\right) \tag{2.25}$$

where A is a proportionality factor and B depends only on particle size but not on temperature or on polymer concentration. The definition of mobility is given by:

$$D = R \cdot T \cdot m_d \tag{2.26}$$

where D is the self-diffusion coefficient of the molecule, T [K] is the temperature and R the gas constant. Finally, using this to equations, we have:

$$D = A \cdot R \cdot T \cdot \exp\left(-\frac{B}{f_v}\right) \tag{2.27}$$

According to Fujita, the free volume theory provided a good agreement with polymer–organic solvent systems whereas polymer–water systems failed because of the numerous interactions between the molecules. Fujita's free volume model seems adequate in the description of the diffusion of small-sized diffusants in dilute and semi-dilute polymer solutions and gels, mostly organic systems. Yasuda et al. (1968) examined the free volume theory of diffusion assuming that free volume of a binary system, as proposed by Fujita, mostly depends on volume fraction of the solvent.

This assumption was based on the fact that:

- polymer was less mobile than solvent;
- effective free volume considered as a contribution from solvent;
- in practice, solvent diffusion decreased with increasing polymer concentration.

Therefore, the total free volume comes from the contributions of both solvent and polymer:

$$f_v = \varphi_s f_s + (1 - \varphi_s) f_P \tag{2.28}$$

where f_v is the total free volume, f_s the free volume contribution from solvent, f_P the free volume contribution from polymer, φ_s the volume fraction of solvent and φ_P the volume fraction of polymer. Substituting this equation into Fujita's one and assuming that there is no interaction between polymer and diffusing molecule, we obtain:

$$\frac{D}{D_0} = \exp\left[-\frac{B}{f_v^*}\left(1 - \frac{1}{1 - \varphi_P}\right)\right] \tag{2.29}$$

where f_v^* is the solvent free volume in polymer solution.

The gap of the free volume concept lies in neglecting screening effects, which here start to occur. Therefore, the model of Yasuda can be used to analyse diffusion data of relatively small-sized diffusants in dilute and semi-dilute polymer systems. Then Vrentas and Duda (1977), Vrentas et al. (1985, 1993) re-examined and improved the free volume model. In particular they extended the free volume theory to a wide range of temperatures and polymer concentrations. The free volume contributions from both solvent and polymer are now taken into account. With numerous improvements, the free volume theory of Vrentas and Duda takes into account several physical parameters such as temperature, activation energy, polymer concentration, solvent size, and molecular weight of the diffusant. If we

consider a binary system (solvent diffusion in a polymer network) the model of Vrentas and Duda is expressed by the following equation:

$$\frac{D}{D_0} = D_{01}\exp\left(-\frac{E}{RT}\right)\exp\left(\frac{\omega_1\hat{V}_1^* + \xi\omega_2\hat{V}_2^*}{K_{11}\omega_1\left(K_{21} - T_{g1} + T\right)/\gamma_1 + K_{12}\omega_2\left(K_{22} - T_{g2} + T\right)/\gamma_2}\right) \tag{2.30}$$

where D_{01} is the solvent self-diffusion coefficient in absence of polymer or a constant pre-exponential factor, E is the activation energy for a solvent jump, ω_i is the weight fraction of component i, $\hat{V}_1^*$ is the specific volume needed for one jumping unit of component i, ξ is the ratio of volume of solvent jumping unit to that of polymer jumping unit.

γ_i represents the overlap factor for the free volume for pure component i, T_{gi} is the glass transition temperature of component i, K_{11} and K_{21} are solvent free volume parameters and K_{12} and K_{22} are polymer free volume parameters. The free volume parameters K_{11} and K_{21} were defined as follows:

$$K_{11} = \hat{V}_1^0 T_{g1}\left[\alpha_1 - \left(1 - f_{H1}^G\right)\alpha_{c1}\right] \tag{2.31}$$

$$K_{21} = \left[\frac{f_{H1}^G}{\alpha_1 - \left(1 - f_{H1}^G\right)\alpha_{c1}}\right] \tag{2.32}$$

where α_1 is the thermal expansion coefficient of solvent, α_{c1} is the thermal expansion coefficient for the sum of specific occupied volume and specific interstitial free volume, $\hat{V}_1^0$ is the free volume occupied by solvent at 0 K, and f_{H1}^G is the average fractional hole free volume. The approach of Vrentas and Duda is based on the following assumptions:

- mixing of polymer and solvent partial specific volumes does not lead to volume change;
- polymer thermal expansion coefficients α_2 and α_{c2} is approximated to average values over temperature interval of interest;
- total hole free volume of the system is computed by using free volume parameters K_{11}/γ_1 and K_{21}/γ_2, which are determined from pure component data for solvent and polymer;
- activation energy for solvent jump, E, depends on polymer concentration since energy per mole needed by solvent molecule to overcome attractive forces depends on its neighbours. Transition from energy in concentrated region to region near pure solvent limit is assumed to be smooth as $\omega_1 \rightarrow 1$.

According to Lodge et al. (1990) Vrentas and Duda's model is successful as a predictive theory over the complete range of polymer concentrations, and over a substantial range of temperatures (above glass transition temperature), whereas other models cannot be used to predict or examine the temperature dependence.

Nonetheless, the model of Vrentas and Duda needs numerous parameters, even 14. Among these 14 parameters 10 need to be evaluated in order to predict self-diffusion coefficient. Furthermore, these parameters are not usually available in literature for many polymers, especially new ones. In addition for the treatment of transport mechanism in cross-linked polymer networks, Peppas (1987) studied nonporous hydrogels, for which space between macromolecular chains is limited and where the mechanism of transport is mainly due to diffusion, and convection is negligible. In pharmaceutical applications such as drug releases, nonporous hydrogels seem to be more often used than porous gels. The model of Peppas and Reinhart is also based on free volume concept: diffusion is said to occur through gel space not occupied by polymer chains. Thus, self-diffusion coefficient of a diffusant is considered proportional to probability of moving through gel with mesh size, P_ξ, but also proportional to probability of finding the required free volume in gel and solution, P'_0/P_0^+, which is given by the following equation:

$$\frac{D}{D_0} = P_\xi \frac{P'_0}{P_0^+} \tag{2.33}$$

where D is the solute diffusion coefficient in hydrogel, D_0 is the solute diffusion coefficient in water. The probability, P'_0/P_0^+, of finding the required free volume was analysed by Peppas and Reinhart (1983). They also assumed that free volume available for solute diffusion was mostly due to water, and only a little contribute from polymer. The following expression was then obtained:

$$\frac{D}{D_0} = P_\xi \exp\left(-\frac{Y}{Q-1}\right) \tag{2.34}$$

where $Y = k_2 R_h^2$ is a structural parameter, k_2 a parameter of the polymer-water system, R_h the solute hydrodynamic radius, and Q the volume degree of swelling for gel.

The probability, P_ξ, of moving through mesh size, ξ, was studied later by Reinhart and Peppas who demonstrated that this quantity is related to a critical mesh size, M_c^*, below which diffusion of a solute of size R_h could not occur:

$$P_\xi = \frac{M_c - M_c^*}{M_n - M_c^*} \tag{2.35}$$

where M_c is the number average molecular weight between cross-links, M_n the number average molecular weight of uncross-linked polymer. Indeed, M_c^* represents the minimal distance in monomer unit between two cross-link points for which diffusion is possible. Combining the equations, diffusion coefficient in highly swollen membranes can be expressed by:

$$\frac{D}{D_0} = k_1 = \frac{M_c - M_c^*}{M_n - M_c^*} \exp\left(-\frac{k_2 R_h^2}{Q-1}\right) \tag{2.36}$$

where k_1 is a structural parameter of polymer-water system.

To describe solute transport in moderately swollen networks, they considered that in a moderately swollen network free volume was not equal to free volume of solvent, and that diffusion jump length of solute in solution was not equal to that of solute in water. A new equation was derived:

$$\frac{D}{D_0} = B(v^*)\frac{\lambda^2}{\lambda_0^2} \exp\left[-v_s \frac{1}{V} - \frac{1}{V_0'}\right] \tag{2.37}$$

where λ^2 and λ_0^2 are the diffusion jump lengths of solute in hydrogel and water, respectively, $B(v^*)$ is a term representing the characteristic size of space available for diffusion in the membrane, v_s is the size of diffusing solute, and V and V_0' are the free volumes in swollen membrane and water, respectively. Peppas has published several papers with diffusants of various sizes in various hydrogels that showed good agreement with the model, but they have also pointed out the limitations of their model.

Mallapragada and Peppas (1997) found that diffusion of ionized diffusants in charged hydrogels is much more hindered than that of larger proteins because of their interactions with ionized carboxylic acid groups.

Thus, a parameter relating interactions between ionized diffusants and network should be introduced. In addition, problems may also occur when diffusant size is close to or larger than mesh size in the network due to screening effects. The free volume models have found various success in the description of diffusion in polymer systems (Table 2.2).

The model of Vrentas and Duda seems to be the most useful as it is applicable over a large range of polymer concentrations and temperatures. However, obtaining the numerous parameters required represent quite a task since these parameters are not always available.

Table 2.2 Obstruction effects models

Authors	Applications
Fujita	Solvents and small-sized diffusants
	Semi-dilute polymer solutions
Yasuda	Solvents and small-sized diffusants
	Semi-dilute polymer solutions
Vrentas and Duda	Various solutes and solvents
	Semi-dilute and concentrated polymer solutions
Peppas and Reinhart	Various solutes and solvents
	Chemically cross-linked gels and hydrogels

2.3.3 Other Models

2.3.3.1 Amsden Model

In Amsden's conception, the obstruction and hydrodynamic models cannot adequately describe diffusion behavior of macromolecules within stiff-chained hydrogels, and the combined obstruction and hydrodynamic theories can provide a better approximation of diffusion data but do not predict the effect of solute radius on its reduced diffusivity. Therefore, Amsden (1998) proposed a new diffusion model based on the equation of Lustig and Peppas. According to Amsden, transport of a molecule through hydrogel is proportional to the probability of finding a succession of holes larger than diffusant diameter.

Thus, the effective diffusivity of diffusant $\overline{D_e}$ can be expressed as:

$$\overline{D_e} = \overline{D_m} \int_{r^*}^{\infty} g(r)dr \tag{2.38}$$

where $\overline{D_m}$ is the average mutual diffusion coefficient of the solute, *g(r)* the distribution of spheres within the hydrogel, and r^* the critical sphere radius required for solute diffusion. In case of straight polymer fibers randomly dispersed in hydrogel network, the distribution of spheres *g(r)* can be expressed as:

$$g(r) = \frac{\pi r}{2R^2} \exp\left[-\frac{\pi}{4}\left(\frac{r}{R}\right)^2\right] \tag{2.39}$$

where *R* is the mean radius of distribution. Using this two equation and carrying out the integration, one can obtain:

$$\overline{D_e} = \overline{D_m} \exp\left[-\frac{\pi}{4}\left(\frac{r^*}{R}\right)^2\right] \tag{2.40}$$

To account for specific polymer thickness, Amsden rewrote this formula to include the average radius of space between polymer chains, $\bar{r}$, and the radius of polymer chain, r_f:

$$\overline{D_e} = \overline{D_m} \exp\left[-\frac{\pi}{4}\left(\frac{r_s + r_f}{\bar{r} + r_f}\right)^2\right] \tag{2.41}$$

$\bar{r}$ can be approximated as the average end-to-end distance between polymer chains, ξ. Further, from scaling concepts ξ was found dependent on the polymer volume fraction and on the radius of polymer chain:

$$\xi = k_1 r_f \varphi^{-1/2} \tag{2.42}$$

where k_1 is a constant for a given polymer-solvent system, dependent on the length of monomer unit and the stiffness or flexibility of polymer chain.

Substitution of this relation leads to the final form of Amsden's diffusion model:

$$\frac{\overline{D_e}}{\overline{D_m}} = \exp\left[-\pi\left(\frac{r_s + r_f}{r_f}\right)^2 \frac{\varphi}{\left(k_1 + 2\varphi^{1/2}\right)^2}\right] \tag{2.43}$$

Thus, this model takes into account the polymer structural properties such as polymer chain stiffness, polymer chain radius, polymer volume fraction as well as size of the diffusant. The model predicts a decrease of solute diffusion when polymer volume fraction increases, when diffusant size increases, and when radius of polymer chain decreases. The dependence of diffusion on the hydrodynamic radius of solute was also predicted properly. Enormous progress has been made in the field but controversies are not uncommon. It seems also fair to say that limitations exist for application of physical models and care should be taken in use of models for the interpretation of results obtained. The rapid development of various techniques such as NMR allows the study of more complicated systems to obtain further information on the properties of the diffusants and polymeric networks.

For example, it is now possible to track the release of solutes such as drugs from a polymer matrix in real-time situations by NMR imaging. Studies of this kind should generate more results, leading to a better understanding of diffusion process in polymer systems.

2.4 Diffusion in Charged Hydrogels

The investigation of hydrogels loaded with charged species, typically salts, has made necessary a better understanding of the electrostatic interactions inside polymer matrices. Numerous analytical separation or preconcentration methods (e.g., diffusion gradient in thin films (DGT) and gel electrophoresis) require controlled diffusion of ionic solutes in organic gels. Diffusion in gels is also an important component in many environmental, pharmaceutical, and biological applications. Even if there is not yet a general theory describing this phenomena, several improvement have been done. Here two of the main works are presented.

2.4.1 Fatin-Rouge Model

Fatin-Rouge et al. (2003) investigated the diffusion and binding properties of an agarose gel, taking in account for the electrical, steric, and chemical interactions.

They tested several substances (Na^+, Li^+, Cl^-, F^-, calcein^{3-},) with fluorescence correlation spectroscopy. The distribution of solute (A) between a charged agarose hydrogel and water can be described by a global partition coefficient, Φ:

$$\Phi = \theta \cdot \alpha \cdot \pi = \frac{[A]_g}{[A]_w} \tag{2.44}$$

where θ, α, and π are the partition coefficients for purely steric, chemical, and electrostatic interactions, respectively, and $[A]_g$ and $[A]_w$ are solute concentrations in the gel and in the external water at equilibrium, respectively.

The steric interactions can be calculated for spherical solutes, with Eq. 2.45:

$$\theta = (1 - \phi) \cdot \left(1 - \frac{R_A}{R_p}\right)^2 \tag{2.45}$$

where R_A is the solute hydrodynamic radius, R_P is the radius of the gel pores, and ϕ is the volume fraction of the polymer in the hydrogel.

The agarose gel contains ionisable groups that can be negatively charged. Fatin-Rouge established that a Boltzmann distribution could be adopted to compute the electrostatic parameter:

$$\pi = \exp\left(-\frac{z_A F \psi}{RT}\right) \tag{2.46}$$

where z_A is the electrical charge of A, ψ is the Donnan potential and F the Faraday constant. The Donnan potential in the agarose gel is related to its charge density (F), the charge density (ρ), the molar concentration (c) of the electrolyte (assumed to be symmetrical) in the external solution, and the charge (z) of the ion of the electrolyte by the following relationship:

$$\psi = \frac{RT}{zF} \sinh^{-1}\left(\frac{\rho}{2zFc}\right) \tag{2.47}$$

For the chemical parameters, Fatin-Rouge supposed a possible complex formation between solute A and gel sites S, expressed by:

$$\alpha = 1 + K_A^{\text{int}}[S] \tag{2.48}$$

where K_A^{int} is an equilibrium constant that includes charge effects, and $[S]$ the sites concentration inside gel. When an agarose gel separates two solutions of different concentrations of solute A, solute A diffuses through the gel from the more concentrated (source) to the less concentrated (receiving) solution. After an initial induction period, a steady-state regime is established, and a linear concentration gradient is set up within the gel. The flux of A within the hydrogel is given by Fick's first law:

$$J = D_g^A \cdot \frac{d[A]_g}{dx} \tag{2.49}$$

where D_g^A is the average diffusion coefficient of A within the gel. This equation can be rewritten as:

$$J = \frac{D_g^A \cdot \left([A]_g^S - [A]_g^r\right)}{m} \tag{2.50}$$

where m is the gel membrane thickness and $[A]_g^s$ and $[A]_g^r$ are the total concentrations of A in the gel at the gel/source and gel/receiving solution interfaces, respectively. The partition coefficient of A at both interfaces of the hydrogel can be rewritten as:

$$\Phi = \theta \cdot \alpha \cdot \pi = \frac{[A]_g^s}{C_S^A} = \frac{[A]_g^r}{C_r^A} \tag{2.51}$$

where C_S^A and C_r^A are the concentrations of A in the bulk source and receiving solutions, respectively, provided that the diffusion boundary layer thicknesses at both interfaces are negligible. Combining the aforementioned equation, we obtain:

$$J = \frac{\Phi \cdot D_g^A \cdot \left(C_S^A - C_r^A\right)}{m} = \frac{dN}{S_m dt} \tag{2.52}$$

where S_m is the gel's surface area. Integrating this equation, in order to compute the flux (N), leads to:

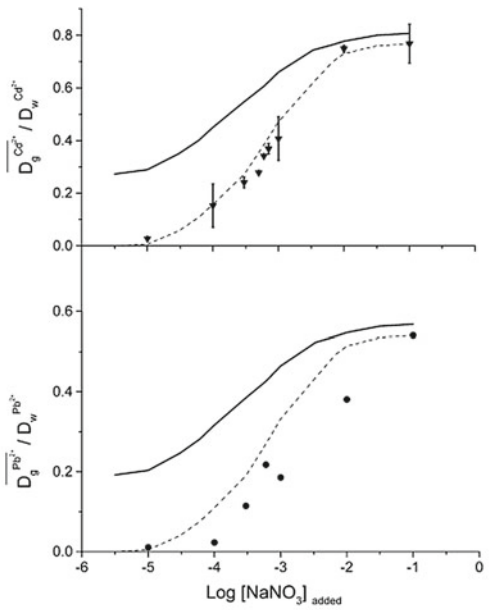
$$N = \frac{s_m \cdot \sigma \cdot \theta \cdot \pi \cdot D_W^A \cdot C_S^A}{m} \cdot t \tag{2.53}$$

Here, σ represents the ratio of the diffusion coefficient of solute A in the gel pores when only steric effects are important, to that in water (D_W), in according to Renkin model (1954). Using this equation Fatin-Rouge computed the ratio D_g^A/D_w^A, to give a better indication of the solute-gel interactions:

$$\frac{D_g^A}{D_w^A} = \frac{sm}{D_w^A \cdot sm \cdot \Phi \cdot C_S^A} = \frac{sm}{D_w^A \cdot sm \cdot \theta\pi\alpha \cdot C_S^A} \tag{2.54}$$

The trend of this ratio is reported in Fig. 2.3:

Figure 2.3 shows that values of the ratio D_g^A/D_w^A for Cd^{2+}, Pb^{2+} increase with the concentration of added salt and tend to a limit value at which the electrostatic interactions are fully screened. Fatin-Rouge et al. suggested that electrostatic attraction with agarose fibers reduces the diffusion of metal ions, in according with



$\bar{D}_g^A/D_w^A$ for Cd^{2+} (▼) and Pb^{2+} (●) as a function of the added salt concentration.

Fig. 2.3 Diffusant diffusivity ratio plotted against salt concentration. Reproduced with permission of (Fatin-Rouge et al. 2003). © American Chemical Society

other previous works. Their model provide in general good predictions of the observed effects of pH and ionic strength on the partitioning and diffusion of small ions. Furthermore, they suggest that local electrostatic potential influences the diffusion of ions in the gel. The results are useful in various applications of agarose gel where pH and ionic strength changes may play important roles such as drug delivery from gel capsules or the use of agarose for in situ environmental analysis (e.g., diffusion gradients in thin films).

2.4.2 Vega Model

Understanding ion diffusion phenomena in biological tissues is important for the study of signal transduction in tissue and cells. In their study, Vega et al. (2003) reported a novel approach to investigate ion diffusion in non-charged porous materials using an electrical conductivity method. They investigated the effect of ionic strength and porosity on ion diffusion (K^+ and Cl^-) in hydrogels. Ion diffusivity is related to electrical conductivity and tissue water content or porosity. By measuring electrical conductivity of various gel concentrations in different bathing solutions, one can determine ion diffusivity as a function of gel porosity and ionic strength. Potassium and chloride ion diffusion coefficients (D±) are related to the

specific electrical conductivity (χ_{gel}), ion concentrations (C±) and volume fraction of water by the following equation:

$$\chi_{gel} = \frac{F_C^2}{RT}\phi^w(C^+D^+ + C^-D^-) \tag{2.55}$$

where F_c is the Faraday constant, R is the gas constant, and T is the absolute temperature. In this case, the positive and negative ion concentrations are the same since the agarose gels used in this study are non-charged. The diffusion coefficients can also be assumed to be the same. Since $C^+ = C^-$ and $D^+ = D^-$, and taking into account the conductivity of the bathing solution, the normalized ion diffusion coefficient in gel (D/D_0) can be obtained by the following equation:

$$\frac{D}{D_0} = \frac{\chi_{gel}}{\chi_0\phi^w} \tag{2.56}$$

where D_0 is the ion diffusion coefficient in solution and χ_0 is the electrical r porosity. By measuring electrical conductivity of various gel concentrations in different bath conductivity of the bathing solution. The ion diffusion coefficient in gel is related to the volume fraction of gel (ϕ^S), the pore size (ξ) of gel and radius of the ion (α), given by:

$$\frac{D}{D_0} = \exp\left(-\alpha \cdot \Phi^{0.5}\right) \tag{2.57}$$

where:

$$\Phi = \frac{a}{\xi}\phi^S \tag{2.58}$$

and α is a parameter. The radii of the ions were calculated using the Stokes-Einstein equation. In summary this study underlined that varying the concentration of the bathing solution does not influence ion diffusion phenomena.

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