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Theoretical Description of Hydrogel Swelling: A Review

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ABSTRACT

During the past decades, hydrogels have been introduced suitable as novel materials for a variety of applications such as biomedical engineering, sanitary products, agriculture, bioseparation, enhanced oil recovery, etc. They have been successfully used as superabsorbent materials and in drug delivery, cell encapsulation and tissue repair due to their high water content and consequent biocompatibility. Considering the fact that water retention in the hydrogels provides a suitable drug diffusion pathway; many hydrogel-based networks have been designed and fabricated as intelligent carriers of drugs. The rate and degree of hydrogel swelling are the most important parameters which control the release patterns of solvents and drugs from these polymeric networks. Therefore, the precise account of hydrogel behaviour as well as mathematical description of equilibrium swelling, dimensional changes due to solvent uptake, desorption and drug release profiles were the main objectives in many investigations. The objective of this manuscript is to give a brief review on existing mathematical models and theories in the field of hydrogel swelling as well as the description of the drug release mechanism from swelling-controlled networks. The most important properties of hydrogels relevant to their swelling behaviour as well as kinetics and thermodynamic of swelling are also presented.

Key Words:

hydrogels;
swelling;
kinetics;
thermodynamics;
drug delivery.

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INTRODUCTION

During the past decades, most of the pharmaceutical research activities have focused on the discovery or synthesis of the novel

drugs and drug administration systems. In this way, controlled release drug delivery systems (DDS) have an outstanding place [1,2]. Among various kinds of polymeric systems, which have

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been used as drug containers or release rate controlling barriers, hydrogels have gained considerable interest and reviewed from different points of view [3-8]. Hydrogels are a unique class of macromolecular networks that may contain a large fraction of aqueous solvent within their structure. They are particularly suitable for biomedical and tissue engineering applications [9-12] because of their ability to simulate biological tissues [13,14] and gained increased applications in bioseparations, agriculture and enhanced oil recovery [15-17]. The hydrophilicity of the network is due to the presence of chemical residues such as hydroxylic (-OH), carboxylic (-COOH), amidic (-CONH-), primary amidic (-CONH₂), sulphonic (-SO₃H), and others that can be found within the polymer backbone or as lateral chains. Nevertheless, it is also possible to produce hydrogels containing a significant portion of hydrophobic polymers, by blending or copolymerizing hydrophilic and hydrophobic polymers.

Considering various advantages, such as biocompatibility, ability to respond to external stimuli under various physiological conditions, and the fact that water retention in the hydrogels provides a suitable drug diffusion pathway [18]; many hydrogel-based networks have been designed and fabricated as intelligent carriers of drugs [19-21].

The hydrophilic/hydrophobic balance of the hydrogels, the degree of cross-linking, and especially, the degree of ionization and its interaction with counterions are the important parameters which control the equilibrium swelling, dimensional change and the release patterns of drugs from these carriers [18]. Hence, mathematical modelling of hydrogel swelling and predictability of swelling behaviour has gained considerable attention during past decades. This article provides a brief review on existing mathematical models and theories which describe equilibrium and kinetics of hydrogel swelling as well as the drug release mechanism from swelling-controlled networks. In spite of numerous published review papers, which focus directly or indirectly on swelling behaviour of hydrogels, the present review aims to throw light on the specific theories which focus on the kinetics and thermodynamics of hydrogel swelling.

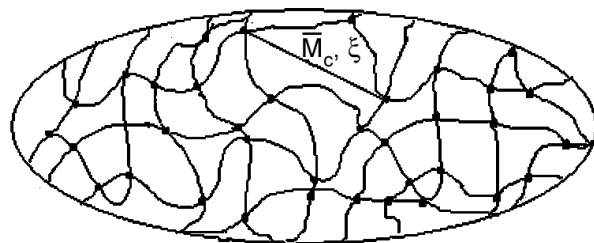


Figure 1. Schematic representation of the cross-linked structure of a hydrogel. $\overline{M}_c$ is the molecular weight of the polymer chains between cross-links and ξ is the molecular mesh size.

NETWORK STRUCTURE OF HYDROGELS

The structure of an idealized hydrogel is shown in Figure 1. The most important parameters that define the structure and properties of swollen hydrogels are the polymer volume fraction in the swollen state, $v_{2,s}$, the effective molecular weight of the polymer chain between cross-linking points, $\overline{M}_c$, and the correlation distance between two adjacent cross-links, ξ [1]. Rubber-elasticity theory and equilibrium-swelling theory are extensively applied to describe these three dependent parameters.

The polymer volume fraction in the swollen state ($v_{2,s}$) describes the amount of liquid that can be imbibed in hydrogels and is defined as a ratio of the polymer volume (V_p) to the swollen gel volume (V_g). It is also a reciprocal of the volumetric swollen ratio (Q) which can be related to the densities of the solvent (ρ_1), polymer (ρ_2) and the mass swollen ratio (Q_m) [22]:

$$v_{2,s} = \frac{V_p}{V_g} = Q^{-1} = \frac{1}{\frac{Q_m}{\rho_1} + \frac{1}{\rho_2}} \quad (1)$$

The effective molecular weight of the polymer chain between cross-linking points is commonly related to the degree of cross-linking in the gel (X) as [23]:

$$X = \frac{M_0}{2\overline{M}_c} \quad (2)$$

where, M_0 is an estimate of the molecular weight of

the repeating units.

ξ is the distance between sequential cross-linking points, which represents an estimate of the available space between the macromolecular chains accessible for the drug diffusion and can be calculated from the following equation [24]:

$$\xi = v_{2,s}^{-1/3} l \left(\frac{C_n \cdot 2\overline{M_c}}{M_r} \right)^{1/2} \quad (3)$$

where C_n is Flory characteristic ratio which is a constant for a given polymer-solvent system, l is the carbon-carbon bond length and M_r is the weight of the repeating units from which the polymer chain is composed.

SWELLING BEHAVIOUR OF HYDROGELS

The favourable property of hydrogels is their ability to swell, when put in contact with a thermodynamically compatible solvent. When a hydrogel in its initial state is in contact with solvent molecules, the latter attacks the hydrogel surface and penetrates into the polymeric network. In this case, the unsolvated glassy phase is separated from rubbery hydrogel region with a moving boundary. Regularly the meshes of the network in the rubbery phase will start expanding, allowing other solvent molecules to penetrate within the hydrogel network. Achilleos et al. have developed a technique for the real-time visualization of dynamic deformation profiles during gel swelling processes (Figure 2) [25]. The system, which is based on caged photo-activated fluorophores covalently attached to the gel network, can provide quantitative information on transport fields such as polymer deformation and concentration. Based on this technique and other simulations [26], it is obvious that swelling is not a continual process. Against the favourable osmotic force, there is an opposite elasticity force, which balances the stretching of the network and prevents its deformation. At the equilibrium, where the elasticity and osmotic forces are balanced, there is no additional swelling.

The evidence of solvent release from a strongly charged polyelectrolyte gel under external compression has been demonstrated experimentally

by Vervoort et al. [27]. Based on their studies, the volume loss occurs at any initial gel swelling degree, even if the gel is far from its equilibrium state. In the case of neutral gels, the repulsion between monomers which is caused by the Van der Waals interactions will be restricted by the applied pressure and results in some decrease of the gel volume. In the case of the polyelectrolyte hydrogels, the applied pressure would be restricted by osmotic pressure of counter-ions, thus leading to a larger solvent release compared to the neutral networks. The solvent release is increased by reducing the polymer concentration. In fact, both the Van der Waals repulsion of monomers and the osmotic pressure of counter-ions would be diminished which lead to a larger compression with a smaller lateral swelling [27].

One of the very important features of hydrogel swelling is the rate of swelling which is determined by several physicochemical parameters particularly the extent of porosity and the type of porous structure. In this relation, hydrogels may be classified into four classes; non-porous, micro-porous, macro-porous and super-porous hydrogels (Table 1).

According to Lowman definition [23], non-porous gels have molecular-sized pores equal to the macromolecular correlation length, ξ (between 10 and 100 Å). The polymer chains of these hydrogels are densely packed and provide strictly limited solute transport via the diffusion through free volumes. Therefore, the ratio of the diffusion coefficient of the solute in the membrane ($D_{2,13}$) to the diffusion coefficient of the solute in the pure solvent ($D_{2,1}$) could be related to the degree of hydration of the membrane, H (g water/g swollen gel) [23]:

$$\frac{D_{2,13}}{D_{2,1}} = \phi(q_s) \exp \left[-B \left(\frac{q_s}{V_{f,1}} \right) \left(\frac{1}{H} - 1 \right) \right] \quad (4)$$

where, the subscripts 1, 2 and 3 represent the water, solute and the polymer. $V_{f,1}$ is the free volume by the water, ϕ is a sieving factor which provides a limiting mesh size below which solutes of cross-sectional area (q_s) cannot pass and B is a parameter characteristic of the polymer.

Assuming the same diffusional jump length of solute in the gel and the pure solvent, Peppas

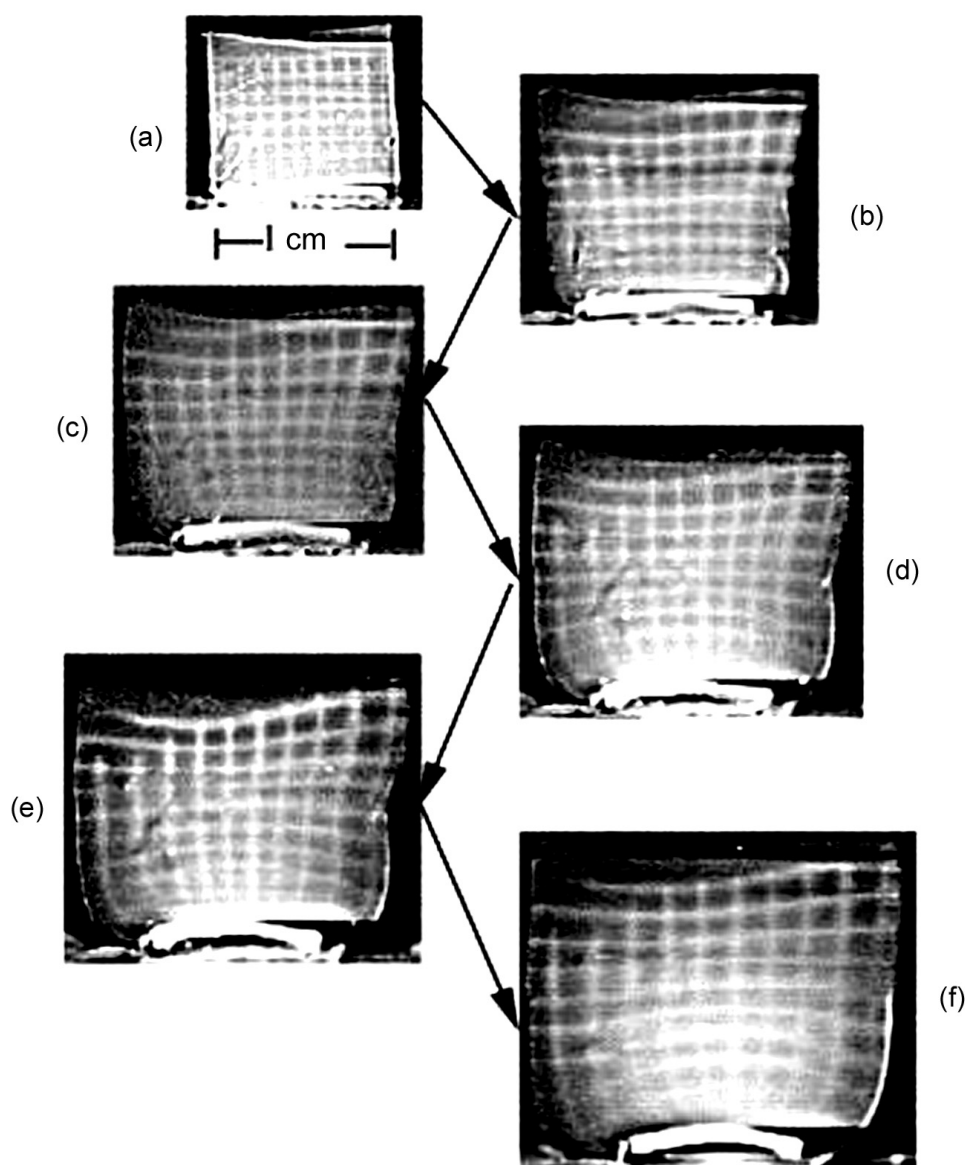


Figure 2. Swelling of an acrylate gel in an aqueous solution with simultaneous visualization of a material grid; the snapshots were recorded at $t =$ (a) 0, (b) 1.25, (c) 2.25, (d) 6, (e) 8.5 and (f) 24 h, respectively. Adopted from Ref [31].

developed the following equation for highly swollen, non-porous hydrogels [23]:

$$\frac{D_{2,13}}{D_{2,1}} = k_1 \left(\frac{\overline{M}_c - \overline{M}_c^*}{\overline{M}_n - \overline{M}_c^*} \right) \exp \left(-\frac{k_2 r_s^2}{Q-1} \right) \quad (5)$$

where k_1 and k_2 are parameters based on the polymer structure, Q is the degree of swelling (g swollen polymer/g dry polymer), r_s is the solute radius, $\overline{M}_c$ is the molecular weight of the polymer chains between

cross-links, $\overline{M}_n$ is the molecular weight of linear polymer chains prepared using the same conditions in the absence of cross-linking agent and $\overline{M}_c^*$ is the critical molecular weight between cross-links below which a solute of size r_s could not diffuse.

The pore size of micro-porous hydrogels is between 100 and 1000 Å [23]. Since the pore size begins to approach the size of the diffusing solutes, the solute transport occurs due to a combination of molecular diffusion and convection in the water filled pores. The ratio of diffusion coefficient in the

Table 1. Hydrogels in a viewpoint of porosity-related swelling kinetics.

Type	Morphology	Type of absorbed water	Major swelling mechanism	Swelling rate	Application
Non-porous	Without network porosity	Mostly bound	Diffusion through free volumes	Very slow, sample size-dependent	Various uses from contact lenses to artificial muscles, etc.
Micro-porous	Various porosity with closed-cell structure (100-1000 Å)	Mostly bound	Combination of molecular diffusion and convection in the water filled pores	Slow, sample size-dependent	Mainly in biomedical applications and controlled release technology
Macro-porous	Various porosity with closed-cell structure (0.1 -1 µm)	Mostly bound	Diffusion in the water filled pores	Fast, sample size-dependent	Mainly in form of superabsorbents in baby diapers, etc.
Super-porous	High porosity with interconnected open-cell structure	Mostly free	Capillary forces	Very fast, sample size-independent	DDS (particularly in the gastrointestinal tract), tissue engineering, etc.

membrane to pure solvent (D_{ip}/D_{iw}) is defined as [23]:

$$\frac{D_{ip}}{D_{iw}} = (1 - \lambda^2)(1 - 2.104\lambda + 2.09\lambda^3 - 0.95\lambda^5) \quad (6)$$

where λ is the ratio of the solute diameter (d_h) to the pore size (ξ).

Macro-porous hydrogels have large pores, usually between 0.1 and 1 µm. Since the pores of these gels are much larger than the diffusing species, the effective solute diffusion coefficient (D_{eff}) can be described by the diffusion coefficient of solute in the water field pores (D_{iw}) [23]:

$$D_{eff} = D_{iw} \frac{K_p \varepsilon}{\tau} \quad (7)$$

where K_p , ξ and τ are the partition coefficient, the network porosity and the network tortuosity, respectively.

In 1999, super-porous hydrogels (SPHs) were introduced as a different category of water-absorbent polymer systems [28,29]. The size of pores in SPHs is usually in the range of several hundred micrometers. Most of the spherical pores inside the

hydrogels are connected to form the open channel system, which acts as a capillary system causing a rapid water uptake into the porous structure [30]. Thereby, SPHs swell in aqueous solution to equilibrium state in a matter of a minute regardless of their size. Such a fast swelling is due to absorption of water by capillary force rather than by simple absorption [30,31]. Conventional SPHs are then characterized by fast swelling, high swelling ratio and weak mechanical properties. Recently, new generation of SPHs was developed to overcome their poor mechanical strength. The second-generation SPH composites (SPHCs) are characterized by fast swelling, medium swelling ratio and improved mechanical properties, while the third-generation SPH hybrids (SPHHs) possess high elastic properties [28].

THEORETICAL DESCRIPTION OF SWELLING

During the past decades, modelling of polymeric networks swelling has been conducted on different scales, based on global macroscopic to microscopic theories [32]. For instance, the global swelling ratio of polyelectrolyte gels is well explained through

statistical theory. Based on this macroscopic theory, the equilibrium state is achieved by a minimum of the Gibbs free energy, ΔF . This theory is applied for chemical and also thermal stimulations [33-35]. As an example, the experimental results of swelling of *N*-isopropyl acrylamide (NIPAAm) hydrogels in water and aqueous solutions of ethanol and acetone are well analyzed by statistical theory [35].

For this purpose, a combination of a model for the Gibbs energy of the fluid phases and an expression for the elastic energy of the network is employed. The influence of total mass fraction of polymerizable material as well as the mole fraction of the cross-linking agent on the degree of network swelling was effectively predicted.

Theory of porous media is an example of macroscopic or mesoscopic continuum theories. This theory is based on the theory of mixtures extended by the conception of volume fractions [36]. Through this homogenized model, all physical and geometrical quantities are considered as the averages of the real data. This theory is formulated simply by conservation equations for the different constituents, while the local porous micro-structure and the real geometrical distribution of all the elements are unknown [37,38].

Multi-field formulation, which is a chemo-electro-mechanical model, is formulated by different balance equations [39,40]. The chemical, electrical and mechanical fields are formulated by the diffusion, the Poisson and the momentum equations, respectively. Commonly, the chemical and electrical fields are solved at the same time. The mechanical displacement comes from the concentration differences in gel and solution.

The discrete element theory describes the micromechanical behaviour of hydrogels. The hydrogel network is characterized by distributed particles interacting with each other mechanically [41]. The mechanical behaviour is obtained by solving the Newton's equations of motion, while the chemical field is described by diffusion equations for the different mobile particles.

Recently, the swelling behaviour of poly-electrolyte gels under electrochemical stimulation was investigated by Wallmersperger et al., applying different modelling strategies [32]. In the statistical

analysis, the porous media and the discrete element theory models, only the hydrogel network was investigated. While in coupled multi-field formulation, the whole gel-solution domain is considered. They showed that during all the time steps of the discrete element stimulation, the direct physical access to the system as well as the representation of large deformations is accessible.

Based on the works of Wallmersperger, a chemo-electro-mechanical model is developed by Li et al., to simulate the swelling and shrinking of hydrogels [42]. The ionic fluxes within both the hydrogel and solution, the coupling between the electric field, ionic fluxes and mechanical deformations of the hydrogel are well accounted in this model. The incorporation of the relationship between the concentrations of the ionized fixed-charge groups and the diffusive hydrogen ion is the main contribution of this model, which follows a Langmuir isotherm into the Poisson-Nernst-Planck system [42].

Lai's group developed a triphasic chemo-electro-mechanical model to describe the behaviour of soft tissues, such as charged-hydrated tissues [43]. This theory was verified for the one-dimensional equilibrium results of swelling, while neglecting geometrical non-linearities. In this model, an assumption of "electroneutrality" condition is made thereby constraining the application range to a few particular cases [44,45].

Kinetics of Hydrogel Swelling

Swelling is a continuous process of transition from unsolvated glassy or partially rubbery state to a relaxed rubbery region. It is well known that sorption processes for polymer-solvent systems frequently do not conform to the behaviour expected from the classical theory of diffusion [46]. Although penetrant sorption by rubbery polymers may be described by Fickian transport with a concentration dependent diffusion coefficient, this description usually is not successful for glassy polymers. The slow reorientation of polymer molecules can lead to a wide variety of anomalous effects for both permeation and sorption experiments, particularly when such experiments are conducted near or below the glass transition temperature (T_g). Based on the Bajpai classification, two basic categories may arise [47]: first, is the

Fickian or Case I transport, which appears when the T_g of polymer is well below the medium temperature. In this case, the polymer chains have a high mobility and the water penetrates easily in the rubbery network. Therefore, the solvent diffusion rate, R_{diff} , is clearly slower than the polymer chain relaxation rate, R_{relax} , ($R_{diff} \ll R_{relax}$). In slab samples, Case I diffusion is characterized by a linear increase of polymer weight gain as a function of the square root of sorption time. It asymptotically approaches a fixed equilibrium value [47]; secondly, it is non-Fickian diffusion, which appears when the T_g of polymer is well above the experimental temperature. In this situation, the polymer chains are not adequately mobile to permit urgent penetration of water into the polymer core [42]. Non-Fickian diffusion processes have been studied by many groups [48-51]. Depending on the relative rates of chain relaxation and diffusion, they commonly classified the non-Fickian diffusion to two subsections: "Case II transport" and "anomalous transport" (Figure 3). Case II transport is dominated when the diffusion is very rapid compared to relaxation ($R_{diff} \gg R_{relax}$), with relaxation occurring at an observable rate. Here, the rate of mass uptake is directly proportional to time.

The anomalous transport is observed when the diffusion and relaxation rates are comparable ($R_{diff} \approx R_{relax}$). Since most polymers swell when they are in contact with certain solvents, one can use Fick's laws with modified boundary conditions and/or a generalized diffusion coefficient to address the non-Fickian behaviour [52].

Numerous mathematical models have been proposed describing the kinetics of hydrogel swelling. The models may be divided into three categories [53]. The Fickian diffusion models apply Fick's laws to the distribution of solvent in a gel sample during swelling or collapse. These models predict that the fractional approach to equilibrium increases linearly with the square root of time up to roughly 0.4 and that the swelling curve, the fractional approach to equilibrium vs. square root of time, is not sigmoidal even if the diffusion coefficient is a function of composition. The collective diffusion models, developed by Tanaka et al., treat the swelling of a gel as the expansion of a network driven by a gradient of stress [54]. These models describe small volume changes, but they fail to predict the sigmoidal swelling curves resulting from large volume change. Sigmoidal experimental swelling curves are often

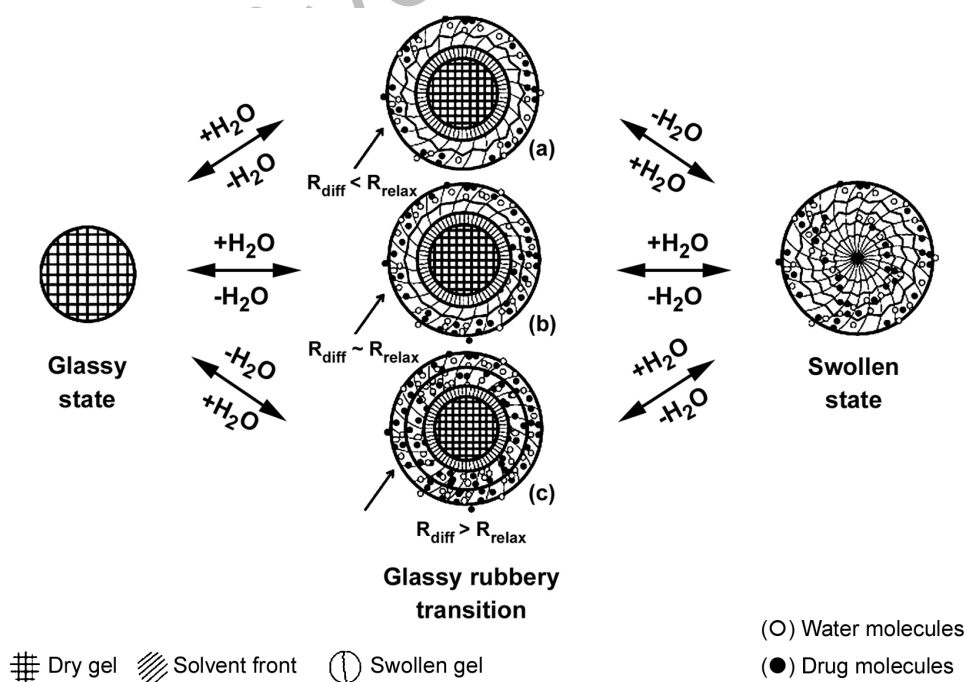


Figure 3. The mechanisms of Case II and anomalous diffusion. Adopted from Ref [52].

taken to indicate non-Fickian behaviour. Deviations from the fixed boundary Fickian behaviour are usually attributed to some of the following phenomena: (i) variable surface concentration, (ii) a history dependent diffusion coefficient, (iii) stresses between parts of the gel swollen to different extents and (iv) polymer relaxation. The first three have been discussed by Crank et al. [55], while the last has been modelled by Joshi et al. [56]. Although these models predict the swelling curves for large volume changes reasonably well, they are subject to three objections: (i) they do not allow for the movement of the gel boundary, (ii) they require three or more parameters to fit experimental data, and (iii) the diffusion coefficients may show unusual composition dependence, e.g. a maximum at an intermediate composition. However it has been shown that the sigmoidal swelling behaviour can be well described by Fickian diffusion when the movement of the gel surface is taken into account correctly [57].

A simple and useful empirical equation, so-called power law equation, is commonly used to determine the mechanism of diffusion in polymeric networks [3]:

$$\frac{M_t}{M_\infty} = kt^n \quad (8)$$

The constants, k and n , are characteristics of the solvent-polymer system. The diffusional exponent, n , is dependent on the geometry of the device as well as the physical mechanism of solute uptake or drug release. Peppas et al. were the first to give an introduction to the use and the limitations of these equations [58]. By determining the diffusional exponent, n , one can gain information about the physical mechanism controlling solute uptake by or drug release from a particular device (Table 1). For a film, $n = 0.5$ indicates Fickian diffusion, $n > 0.5$ indicates anomalous transport and $n = 1$ implies case II (relaxation-controlled) transport.

For Fickian diffusion, the n values close to 0.5 or over 0.5 have been reported in the most published articles [59], while fewer articles have reported the case of $n < 0.5$ [60-63]. The Fickian diffusion, actually, refers to a situation where water penetration rate in the gels is less than the polymer chain relaxation rate. Therefore, $n = 0.5$ indicates a perfect

Table 2. Drug transport mechanisms and diffusional exponents for hydrogel slabs [23].

Type of transport	Diffusional exponent (n)	Time dependence
Fickian diffusion	0.5	$t^{1/2}$
Anomalous transport	$0.5 < n < 1$	t^{n-1}
Case II transport	1	Time independent

Fickian process [64]. Nevertheless, when the water penetration rate is much below the polymer chain relaxation rate, it is possible to record the n values below 0.5. This situation, which is still regarded as Fickian diffusion, is named as "Less Fickian" behaviour [59].

The previously discussed power law equation, even though effectively describes the major portion of the swelling behaviour, fails to give a precise analysis above $M_t/M_\infty = 0.60$ [65]. To obtain a better model beyond 60%, the Berens-Hopfenberg proposed the following differential equation [66]:

$$dM_t/dt = k_2(M_\infty - M_t) \quad (9)$$

where k_2 (min^{-1}) is the relaxation rate constant. The integration of eqn (9) leads to [66]:

$$M_t/M_\infty = (1 - Ae^{-k_2t}) \quad (10)$$

where A is a constant. Here, the constants A and k_2 are calculated from the slopes and intercepts of the plot of $\ln(1 - M_t/M_\infty)$ versus time t at times later than those corresponding to $M_t/M_\infty = 0.60$.

For the case of anomalous transport, Peppas et al. developed the following model to describe the release behaviour of dynamically swelling hydrogels [67]:

$$\frac{M_t}{M_\infty} = k_1t + k_2t^{1/2} \quad (11)$$

This expression describes the release rates in terms of relaxation-controlled transport process, k_1t , and the diffusion-controlled process, $k_2t^{1/2}$.

A non-Fickian diffusional behaviour is observed in the acrylamide-hydroxyethyl methacrylate (AAM-HEMA) hydrogels [68]. Hydrogels with different

molar ratios of AAm to HEMA, have been prepared by redox polymerization method. To increase the micro-porosity of the polymeric network, PEG 4000 was added to the monomers. Based on the swelling experiments, it is also observed that swelling of hydrogels increased with decreasing total monomer, HEMA and cross-linker concentrations, and it decreased with decreasing the content of PEG 4000 in hydrogels [68].

Swelling behaviour of superabsorbent acrylamide/sodium acrylate hydrogels have been studied by Karadag et al. [69]. Different cross-linkers such as trimethylolpropane triacrylate, ethylene glycol dimethacrylate (EGDMA), 1,4-butanediol dimethacrylate and *N,N'*-methylenebisacrylamide were used in copolymerization procedure. The research involved the study of the influence of cross-linkers and the relative content of sodium acrylate on swelling, initial swelling rate, swelling rate constant, swelling coefficient and diffusional behaviour of water in the hydrogel. Their results indicated that due to the presence of ionic groups in acrylamide-sodium acrylate hydrogels, they showed greater swelling in water compared to acrylamide hydrogels and the water intake of hydrogels followed non-Fickian type diffusion [69].

In order to study the equilibrium swelling and kinetics of pH sensitive ionic hydrogels, De et al. synthesized homogeneous copolymers of HEMA (hydroxy-ethyl-methacrylate) and acrylic acid with 1% of a diacrylate cross-linker [70]. Equilibrium and kinetic models were developed and compared with the experimental results. The models were accurate in predicting the swelling processes. In their model, they describe the swelling process as chemo-electro-mechanical model and the kinetics of swelling is limited by diffusion. Results indicated that swelling can be improved by increasing the fixed charge or lowering the ionic strength of the solution. Their study also revealed that Young's modulus changed greatly with the pH of the solution while Poisson's ratio remained unchanged [70].

The transport of solutes into or out of a polymeric hydrogel is essentially controlled by swelling and shrinking of polymeric hydrogels. Grimshaw et al. have presented a macroscopic model predicting the kinetics of swelling in polyelectrolyte gel membranes [71]. Ionic transport within the membrane and

dissociation of fixed charge groups are described by electrochemical equations, while intra-membrane fluid flow and mechanical deformation of the membrane matrix are incorporated in electro-mechanical equations. The chemical and mechanical equations are coupled with chemically dependent swelling forces. The experimental data on chemically and electrically induced swelling and deswelling of PMAA membranes were used to justify the model predictions. They found that diffusion-limited reaction of H^+ ions with hydrogel charge groups dominates deceleration of gel swelling, while mechanical limitations govern acceleration of gel shrinking [71].

Ying et al. showed that the swelling kinetics of the hydrogels based on *n*-alkyl methacrylate esters, acrylic acid, and acrylamide cross-linked with 4,4'-di(methacryloylamino) azobenzene are in good agreement with Schott's second-order diffusion kinetics, which is written as [18]:

$$dM / dt = K_s (M_\infty - M)^2 \quad (12)$$

where M_∞ , M and K_s are the maximum or equilibrium water uptake, the water uptake at time t , and the kinetic rate constant of swelling, respectively. After definite integration by the application of the initial conditions: $M = 0$ at $t = 0$ and $M = M$ at $t = t$, eqn (7) becomes [18]:

$$t / M = A + Bt \quad (13)$$

where $A = 1/K_s M_\infty^2 = 1/(dM/dt)_0$ is the reciprocal of the initial swelling rate of the hydrogel and $B = 1/M_\infty$ is the inverse of the maximum water uptake. Rearranging and differentiating eqn (13) gives the following results [18]:

$$dM / dt = A / (A + Bt)^2 \quad (14)$$

This equation indicates that the swelling rate is a function of the treatment time. The balance of hydrophobicity/hydrophilicity, the rigidity/flexibility, and the degree of cross-linking will determine the constants A and B of Schott's kinetics equation. However, the degree of cross-linking, the lengths of the *n*-AMA side chains and pH values of medium have the greatest influence on the swelling behaviour

of the gels.

In an interesting work, swelling kinetics of acrylamide/crotonic acid (AAm/CA) hydrogels was studied by Karadag et al. [72]. For this purpose, superswelling AAm/CA hydrogels were prepared by free radical polymerization. For each copolymerization, different compositions of CA and a concentration of multi-functional cross-linkers were used and their roles on the swelling properties were examined. The values of initial swelling rate, swelling rate constant, maximum equilibrium swelling and diffusion coefficients of hydrogels were calculated from the swelling kinetic studies. They have also determined the swelling power number (n), applying the following equation [72]:

$$\frac{M_t - M_0}{M_0} = Kt^n \quad (15)$$

where M_t is the mass of the swollen gel at time t , and M_0 is the mass of the dry gel at time 0. Based on the values of n , which range generally between 0.60 and 0.72, they found that the water uptake of their hydrogels followed non-Fickian type diffusion.

The dynamic swelling behaviour of pH-sensitive hydrogels based on methacrylic derivatives was investigated by Bartil et al., to determine the mechanism of water transport through these hydrogels [65]. They found that the mechanism of water transport was significantly affected by the pH of the swelling medium. At pH 7.0 the transport mechanism was dominated by case II (relaxation controlled), whereas at pH 1.2, the mechanism was non-Fickian (anomalous) transport. The relative contribution of penetrant diffusion and polymer relaxation governs the dynamic swelling behaviour of cross-linked polymers. In ionic polymer networks, relaxation is extensively affected by ionization of the functional groups. Therefore, as gel ionization becomes prominent at pH 7, the swelling mechanism becomes more relaxation-controlled. In contrast, the ionization was not significant at pH 1.2 and the overall transport mechanism was controlled by both diffusion and relaxation at pH = 1.2. Consequently, the predominant mechanism was a non-Fickian (anomalous) transport. A similar study has been done by Kim et al. and the same conclusion has been derived on the swelling behaviour of pH-sensitive

anionic hydrogels used for protein delivery [73]. In another work, the swelling behaviour of alginate-*N,O*-carboxymethyl chitosan (NOCC) gel beads coated by chitosan was investigated by Dolatabadi-Farahani et al. [74]. Their studies showed that swelling degree at pH 7.4 was considerably higher than that at pH 1.2, which indicates the pH sensitivity of these networks. Swelling degree of beads also decreased by chitosan coating and presence of NOCC due to the hydrogen bond formation and ionic interaction of functional groups of the polymer chains.

Swelling behaviour of poly((2-dimethyl amino) ethyl methacrylate-*co*-butyl methacrylate) was investigated by Emileh et al. [75]. These hydrogels demonstrated dual sensitivity towards pH and temperature. It was shown that the pH-sensitive or temperature-sensitive phase transition behaviour of the gels can be changed by changing the temperature or pH of the swelling medium at constant hydrogel composition. Increasing the temperature decreased the transition pH of the pH-sensitive phase transition. While, increasing the pH of the surrounding medium decreased the transition temperature of the temperature-sensitive phase transition. Incorporation of butyl methacrylate in the gel structure has a significant effect on the transition point of the gel. Increasing the butyl methacrylate content of the hydrogel chemical structure reduces the pH and temperature of the pH and temperature-sensitive phase transition points, respectively. The similar effect of increasing temperature or butyl methacrylate content can be explained by the role of hydrophobicity in the phase transition behaviour of hydrogels. The results of equilibrium swelling and compression-strain measurements were used to calculate the polymer-solvent interaction parameters of these hydrogels using the Flory-Rehner equation of equilibrium swelling [75].

Thermodynamics of Equilibrium Swelling of Hydrogels

The thermodynamics of gel swelling has been investigated for many years. Interest in this subject accelerated in the late 1970s upon reports by Tanaka et al. of swelling/collapse phenomena in polyacrylamide gels reminiscent of vapour/liquid phase transition [76]. They assumed that the generation of

stress as well as a drag forces between the network and the solvent counterbalance the motion of the polymer network. The Tanaka group showed that thermo-responsive ionic gels exhibit a discontinuous transition in contrast to a continuous transition exhibited by non-ionic gels. They also reported that deswelling rate of the ionic gels is inversely proportional to the square of the smallest dimension of the material [77]. Dušek et al. [78] anticipated this behaviour earlier. In their theoretical calculations, they expected that the critical conditions for the phase transition of free swelling gel can be achieved by adjusting cross-linking of polymeric gel and dissolved solvent quality. In contrast to free swelling gel, they also suggested that the phase transition of polymer network under the tensional condition can be achieved [78]. Flory's treatment of the thermodynamics of gel swelling was the basis for subsequent work [79]. Many researchers attempted to modify Flory's theory for quantitative prediction of equilibrium swelling phenomena.

The structure of hydrogels that do not contain ionic moieties can be analyzed by the Flory-Rehner theory [80]. Based on this theory, the thermodynamic force of mixing and the retractive force of the polymer chains are the two opposing forces compromising the swelling behaviour in a hydrogel. The Gibbs free energy equation can be used to describe this situation:

$$\Delta G_{total} = \Delta G_{mix} + \Delta G_{el} \quad (16)$$

where ΔG_{total} is the change of total free energy in hydrogel, ΔG_{mix} is the change of free energy of mixing, and ΔG_{el} is the change of elastic free energy. Considering that these two contributions are equal at equilibrium, an expression for determining the molecular weight between two adjacent cross-links of a neutral hydrogel prepared in the absence of a solvent is derived [81]:

$$\frac{1}{\bar{M}_C} = \frac{2}{\bar{M}_n} - \frac{\left(\frac{\bar{v}}{V_1}\right) \left[\ln(1 - v_{2,s}) + v_{2,s} + \chi_1 v_{2,s}^2 \right]}{\left(v_{2,s}^{1/3} - \frac{v_{2,s}}{2} \right)} \quad (17)$$

where, $\bar{M}_n$ is the molecular weight of the polymer chains prepared under identical conditions but in the absence of the cross-linking agent, v is the specific volume of the polymer and V_1 is the molar volume of water. In the case of ionic polymers, the swelling equilibrium of the polymeric matrix is more complicated as it heavily depends also on the ionization degree of the polymer chains and ionic strength of the external solution. The free energy change of ionic hydrogel, corresponding to the volume change during swelling, ΔG_{total} , is the sum of contributions due to mixing of pure solvent with an initially pure, amorphous, unstrained gel network, ΔG_{mix} , due to configurational changes of the gel structure, ΔG_{el} , and due to mixing of ions with solvent, ΔG_{ion} :

$$\Delta G_{total} = \Delta G_{mix} + \Delta G_{el} + \Delta G_{ion} \quad (18)$$

An ionic gel is subjected to a swelling pressure, π , which is expressed as the sum of three components corresponding to each contribution to ΔG [82,83]. The equilibrium condition is obtained when π is set equal to zero.

$$\pi = \pi_{mix} + \pi_{el} + \pi_{ion} = - \left(\frac{\partial \Delta G}{\partial V} \right)_{T, n_i} \quad (19)$$

The osmotic pressure of a polymer solution, π_{mix} , is given by the Flory-Huggins theory [79]:

$$\pi_{mix} = - \frac{RT}{V_1} \left[\ln(1 - v) + v + \chi v^2 \right] \quad (20)$$

where v is the polymer volume fraction and V_1 is the molar volume of the solvent.

The configurational contribution, π_{el} , is evaluated from the configurationally free-energy change, ΔG_{el} , during swelling. Assuming isotropic swelling, by differentiating ΔG_{el} with respect to volume and expanding the inverse Langevin function in a power series, π_{el} is obtained as [82]:

$$\pi_{el} = -v_0 RT \left[\left(\frac{v}{v_0} \right)^{1/3} - \frac{1}{2} \left(\frac{v}{v_0} \right) \right] - v_0 RT \left[\frac{3}{5} (v_0/v)^{1/3} \times \frac{1}{n} + \frac{99}{175} (v_0/v) \frac{1}{n^2} + \frac{513}{875} (v_0/v)^{5/3} \frac{1}{n^3} + \dots \right] \quad (21)$$

where $v_0 = v_0 v_d$ is the concentration of constituent chains at gel formation.

The ionic contribution to the osmotic pressure, π_{ion} , attributed to the difference between the osmotic pressure of the mobile ions in the gel and in the external solution is given by [82]:

$$\pi_{ion} = RT \left[\Phi \sum_i \bar{C}_i - \phi \sum_i C_i \right] \quad (22)$$

where C_i and $\bar{C}_i$ are the concentrations of mobile ions in the external solution and in the gel, ϕ and Φ are the corresponding osmotic coefficients, respectively. Charged groups attached to the network play an essential role in swelling phenomena.

To account for the non-ideal behaviour of the polyelectrolyte gel, an osmotic coefficient for the gel phase is defined as $\Phi = \pi_p / \pi_{ideal}$. The ideal osmotic pressure of the salt-free polyelectrolyte solution is given by the Van't Hoff expression, $\pi_{ideal} = RT(n_m \alpha + n_p)$, where, n is the molarity of the monomer, α is the degree of ionization and n_p is the molarity of the polymer [82]. Since polyelectrolytes are strongly non-ideal, a correction factor, ϕ_p , called the osmotic coefficient, is introduced [82]:

$$\pi_p = RT(n_m \alpha \phi_p + n_p) \quad (23)$$

Combination of above equations will result in [82]:

$$\Phi = \left(\phi_p + \frac{n_p}{n_m \alpha} \right) / \left(1 + \frac{n_p}{n_m \alpha} \right) \quad (24)$$

Considering the above discussion, the swelling behaviour of anionic and cationic hydrogel in electrolyte solutions of different pH and salt concentrations was investigated by Vasheghani-Farahani et al. [82]. They have found that the degree of swelling of an ionic gel in a salt solution is determined largely by the concentration of the mobile counterions. At a fixed composition, counter-ions of higher charge cause a larger shrinkage of the gel. They also showed that thermodynamic model based on Flory's theory and an additive rule for the osmotic pressure of polyelectrolyte-salt solutions could describe the effect of salt on the swelling of ionic gels. They have also assumed that the ideal Donnan

theory could be used to determine the concentration of counterions in the gel phase when the external solution contains both mono- and bivalent counterions. According to their assumptions [82]:

$$\pi_3 = RT \left\{ \Phi \left[n_m \alpha (1+f) / 2 \right] + \phi \sum_{i=1}^n C_i \right\} \quad (25)$$

These theoretical predictions agreed with the experimental results for swelling of ionic gels in monovalent salt solutions. The effect of bivalent counterions on the swelling of ionic gels was also well represented by their proposed model for swelling of ionic gels in electrolyte solutions [82]. It is shown that, starting from the above assumptions and neglecting non-Gaussian term of rubber elasticity and ideal solution assumption, the equilibrium conditions of a polyelectrolyte gel/solution system can be derived from [83]:

$$\begin{aligned} \frac{\Delta\mu}{RT} = & \ln(1-\phi_2) + \phi_2 + \chi\phi_2^2 + \rho_x V_1 (\phi_2^{1/3} - 0.5\phi_2) \\ & + V_1 \left[2c_s^* - \sqrt{\left(\frac{i\phi_2}{V_u} \right)^2} + 4(C_s^*)^2 \right] = 0 \end{aligned} \quad (26)$$

where i is the ionization degree multiplied by the valence of the ionizable chain groups, C_s^* is the salt concentration in the gel phase and V_u is the molar volume of the monomer, respectively. Consequently, the cross-link density, ρ_x , and the intermolecular interactions between polymer segments and solvent molecules are the two important parameters which dominate the swelling state of the hydrogel.

In 1984 Ricka and Tanaka investigated the quantitative consistency of Donnan theory of swelling for weakly charged ionic gels. Swelling experiments as a function of ionic composition of the solvent were carried out on polyacrylamide-acrylic acid copolymer gels. They were able to predict quantitatively the ionic solvent compositions at which the swelling of gels was at its maximum value. The study was valid for gels that did not contain multivalent salts [84].

The phase behaviour of polyelectrolyte hydrogels has been examined as a function of relative charge

composition, bath salt concentration, and solvent quality by English et al. [85]. Sodium chloride and calcium chloride were the salts used for the study. A discontinuous first order swelling transition as a function of bath salt concentration was recorded for 2-hydroxyethyl methacrylate (HEMA) an methacrylic acid (MAAc) copolymer hydrogels. A modified Flory-Huggins model was used to describe this instability behaviour. The role of ion dissociation equilibrium in changing from local or smooth transitions to non-local or discontinuous swelling transitions is illustrated within the framework of their model.

Fernández-Nieves et al. [86] and Routh et al. [87] introduced their thermodynamic analysis for hydrogels based on the combination of Flory-Huggins theory and an elastic term. The Flory-Huggins model is used to describe the mixing of gel network and solvent. It is well known that the interaction parameter between polymer and solvents is both temperature- and concentration-dependent, whereas, this parameter is only considered as temperature dependent in Flory-Huggins model due to the mean field approximation. On the other hand, all volume transition behaviours were observed only in the hydrogels with the lower critical temperature (LCST) so far, and Flory-Huggins theory cannot describe the LCST phase behaviours of polymer solution.

The experimental swelling data obtained from poly(acrylamide-co-sodium acrylate) hydrogels were compared with the predictions of the Flory-Rehner theory of swelling equilibrium [88]. In this interesting study, the ideal Donnan equilibria as well as the effective charge densities were taken into account. The swelling capacities of the hydrogels were measured in water and in aqueous NaCl solutions with different concentrations. Based on the above assumptions, the swelling behaviour of copolymers in water and in aqueous salt solutions was predicted correctly.

In polymeric networks, thermodynamic interaction is indicated by χ , which designates the change in the interaction energy when the polymer and solvent are mixed together [59]. The low value of χ , means a strong interaction between the polymer and water and a weak interaction between hydrophobic

groups of the polymer chains. Erman et al. showed the major role of χ parameter in the thermodynamics of swollen networks [89]. According to the literature, the value of χ can be calculated as [59]:

$$\chi = -\frac{\ln(1-\phi_2) + \phi_2 + v_e V_1 (\phi_2^{1/3} - 2\phi_2 f^{-1})}{\phi_2^2} \quad (27)$$

where v_e is the effective cross-link density in the hydrogel; V_1 is the molar volume of water and f is the functionality of the cross-linker.

The measurement of equilibrium swelling of polymeric networks is an appropriate experimental procedure for the determination of the χ parameter. Using this technique, Bahar et al. found an expression of the form $\chi = 0.49 - 0.25 v_2$ for poly(2-hydroxyethyl methacrylate) gels where v_2 is the polymer volume fraction [90]. In 1990, Davis et al. proposed that the relationship between the χ value and temperature could be fitted well by second degree polynomials as [91]:

$$\chi = a_0 + a_1 T + a_2 T^2 \quad (28)$$

where a_0 is proportional constant which correlates diffusion process, while a_1 and a_2 are constants related to temperature. The total interaction parameter χ is composed of enthalpic (χ_H) and entropic (χ_s) contributions, which can be obtained with the following equations [59]:

$$\chi_H = -T(dx/dT) = T(a_1 + 2a_2 T) \quad (29)$$

$$\chi_s = \chi + T(dx/dT) = \chi + T(a_1 + 2a_2 T) \quad (30)$$

According to the values of χ_H and χ_s at various temperatures, the actual partial molar enthalpy of dilution ($\overline{\Delta H_1}$) and partial molar entropy of dilution ($\overline{\Delta S_1}$) at different temperatures can be obtained with eqns (12) and (13) [59]:

$$(\overline{\Delta H_1}) = RT\phi_2^2 \chi_H \quad (31)$$

$$(\overline{\Delta S_1}) = R\phi_2 (0.5 - \chi_s) \quad (32)$$

Based on these equations, the values of $(\overline{\Delta H_1})$ and $(\overline{\Delta S_1})$ for PEMA and HEMA60/St40 copolymers were calculated. The values were negative, and their absolute values increased with the temperature. The decrease in entropy could be attributed to the structuring of water, which is more manifested upon the solvation of hydrophobic groups. Therefore, hydrogen bonding and hydrophobic interaction will increase. Simultaneously, the increase in water structuring and enhancing in hydrogen bonding will result in decreased enthalpy. For PHEMA and HEMA60/St40, the absolute values of $(\overline{\Delta H_1})$ and $(\overline{\Delta S_1})$ increased with temperature, and this meant that the fraction of structured water increased with decreasing total water content at elevated temperatures. This phenomenon was more obvious for PHEMA than for HEMA60/St40 because of the greater hydrophilicity of PHEMA.

Based on the above theory, polynomial coefficients for χ as a function of temperature for p(2-hydroxyethyl methacrylate/itaconic acid) p(HEMA/IA) hydrogels were calculated [90]. To do this, swelling and thermodynamic properties of PHEMA and copolymeric P(HEMA/IA) hydrogels with different IA contents were studied in a wide pH and temperature range. The enthalpy of mixing ΔH_{mix} and the values of the diffusion coefficients (D) have also been calculated using the Gibbs-Helmholtz equation and dynamic swelling studies, respectively. The obtained results clearly suggest that the increase in temperature causes an increase in the rate of fluid uptake by hydrogels. This may be attributed to the fact that temperature increase causes an increase in the penetration rate of fluid into the gel matrix [90]. Recently, Karimi et al. introduced the applicability of vapour pressure osmometry (VPO) to determine χ parameter in a ternary system [92]. To do this, they investigated various polymer solutions containing high-molecular weight polymers in the semi-diluted concentration range. The theoretical basis for the data evaluation is the Flory-Huggins (FH) model and a virial expansion up to the third virial term. For validation already well characterized polymer/solvent systems poly(vinylpyrrolidone)/water, poly-sulphone/*N,N*-dimethylformamide (DMF) and poly(ether sulphone)/DMF were investigated. In the

second part, interaction parameters of poly(ether imide) (PEI) in solvents with technical relevance for membrane formation (DMF, *N*-methylpyrrolidone (NMP) and *N,N*-dimethylacetamide (DMAc)) were examined at different concentrations and temperatures. Their results indicated that VPO is a promising method for characterization of semi-diluted polymer solutions containing polymers with higher molecular weight [92]. In another work, the rubber-elasticity theory was applied to evaluate χ of Pluronic F127 hydrogels by Mawad et al. [93]. Cylindrical hydrogels at different concentrations (10-25% w/w) were subjected to compression tests by using a computer-interfaced tensiometer (Instron Mini 55, MA, USA). The effective network chain density (ν_e/V_0) was calculated from the slope of the stress-strain plot [93]:

$$\tau_s = \left(\frac{\nu_e}{V_0} \right) RT \nu_{2s}^{1/3} \nu_{2r}^{2/3} (\alpha - \alpha^2) \quad (33)$$

where R and T are the gas constant and absolute temperature; τ_s and α are the applied force per unit area of the swollen hydrogel and the deformation ratio; ν_{2s} and ν_{2r} are the polymer volume fraction in swollen hydrogels and the polymer volume fraction in the hydrogel in its relaxed state, respectively. Having the ν_e/V_0 , the polymer-solvent interaction parameter could be calculated by eqn (6) [93]:

$$\ln(1 - \nu_{2s}) + \nu_{2s} + \chi \nu_{2s}^s + V_1 \left(\frac{\nu_e}{V_0} \right) \left(\nu_{2s}^{1/3} \nu_{2r}^{2/3} - \frac{\nu_{2s}}{2} \right) \quad (34)$$

where V_1 is the molar volume of the solvent water (18 cm³/mol). Based on the results of tensile tests, Mawad et al. proved the Pluronic hydrogels were elastic and their χ values ranged between 0.50 and 0.53, in agreement with the presence of a hydrophobic segment in the polymer chain.

Swelling-controlled Drug Delivery Systems

A swelling-controlled matrix used in drug delivery system must have satisfactory swelling properties, good compression characteristics and high capacity of drug loading. The degree and time of swelling are one of the most important characteristics, which

have a significant effect on the release kinetic of loaded drugs from swelling-controlled systems. The diffusional Deborah number, D_e , which relates water motion to the rate of polymer relaxation, and the swelling interface number, S_w , which measures water penetration into a network relative to diffusion of a dispersed drug out of the polymer, are the two dimensionless parameters that describe the dominant behaviour of swelling-controlled systems [94]. If the swelling process is subjected by water diffusion ($D_e \ll 1$ or $S_w \gg 1$) the Fickian diffusion dominates the drug release process. If the swelling process is controlled by the relaxation time ($D_e \gg 1$ or $S_w \ll 1$), the Case II transport is dominated and results in zero-order release kinetics. However, if D_e or S_w is on the order of 1, the two processes will occur on the same time scale, resulting to anomalous transport behaviour.

Considering three moving boundaries, usually termed as the rubbery, glassy and erosion fronts, results in complicated mathematical equations. In a simple manner, transport phenomenon in a swelling plane can be described by Fick's law, considering a position-dependent diffusion coefficient [94]:

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x} \left(D \frac{\partial C}{\partial x} \right) \quad (35)$$

Defining x as the axial coordinate through which diffusion occurs and C_0 as the initial solute concentration, initial and boundary conditions are [94]:

$$\begin{aligned} \text{at } t = 0 &\rightarrow C(x, t) = C_0 \\ \text{at } x = \delta(t) &\rightarrow C = C_b \end{aligned} \quad (36)$$

$$\text{at } x = 0 \rightarrow \partial C / \partial x = 0$$

Here, $\delta(t)$ and C_b represent the distance from the centre of the sample to its surface and the bulk concentration at the surface of the polymer, respectively. This equation has been solved to give [94]:

$$\frac{M_t}{M_\infty} = 4 \left[\frac{Dt}{l^2} \right] \left[\frac{1}{\pi^{1/2}} + 2 \sum_{n=1}^{\infty} (-1)^n \operatorname{ierfc} \left(\frac{nl}{2\sqrt{Dt}} \right) \right] \quad (37)$$

For short times approximation, this equation leads to the square root of time dependence observed in Fickian diffusion [94]:

$$\frac{M_t}{M_\infty} = 4 \left[\frac{Dt}{\pi l^2} \right]^2 \quad (38)$$

In another approach, Hopfenberg et al. [95] derived a more complicated equation, by separating the stress relaxation terms from diffusive flux. However, their model fitted the experimental data; it needed many fitting parameters and required fine information about relaxation processes.

Recently, transport phenomena in a swellable matrix have been modelled by Brazel et al. by considering concentration-dependent diffusion equations for water (C_1) and drug (C_3) in polymer (subscript 2) [94]:

$$\frac{\partial C_1}{\partial t} = \frac{\partial}{\partial x} \left(D_{1,2} \frac{\partial C_1}{\partial t} - v C_1 \right) \quad (39)$$

$$\frac{\partial C_3}{\partial t} = \frac{\partial}{\partial x} \left(D_{3,2} \frac{\partial C_3}{\partial t} \right) \quad (40)$$

where v represents the swelling front velocity. They assume that the diffusivity of water or drug is significantly different between the glassy and rubbery regions. Therefore, concentration-dependent diffusion coefficient of water and drug were taken as given by Fujita [96]:

$$D_{i,2} = D_i^0 \exp \left[-\beta \left(1 - \frac{C_i}{C_{ie}} \right) \right] \quad (41)$$

where i represents the penetrating species (water or drug), D_i^0 is the diffusion coefficient of water or drug through the swollen gel, β_i is a material constant derived from free volume theory with approximate values between 2 and 7, and c_i/c_{ie} represents the water or drug concentration normalized with respect to the equilibrium concentration. Based on Fujita model description, the drug diffusion coefficient is related to the volumetric and free-volume properties of all components. These equations were solved with an appropriate boundary condition incorporating a relaxation-dependent

Deborah number, $De(\delta_r)$. δ_r is the gel layer thickness which is defined as $\delta(t) - \delta_g(t)$, where $\delta(t)$ is the distance from the gel/water edge to the centre of the hydrogel, and $\delta_g(t)$ is the distance from the centre of the hydrogel to the interface between glassy and rubbery regions of the material (Figure 4). This model clearly demonstrated the effects of plane thickness, water and drug diffusion coefficients and hydrogel relaxation time on the resulting swelling and release profiles [94].

Mathematical modelling of a water-soluble small molecular drug release via a highly swellable and dissolvable polyethylene oxide matrix was developed by Wu et al. [97]. Applying the Fujita theory for diffusion coefficient, they considered the Fick's second law for cylindrical coordinate systems for both axial and radial mass transfer [97]:

$$\frac{\partial C_i}{\partial t} = \frac{1}{r} \frac{\partial}{\partial r} \left(r D_i \frac{\partial C_i}{\partial r} \right) + \frac{\partial}{\partial z} \left(D_i \frac{\partial C_i}{\partial z} \right) \quad (42)$$

where $i = 1$ is for water and $i = 2$ is for caffeine, C_i is the mass concentration of component i within the matrix, r denotes the radial coordinate, z is the axial coordinate and t represents time.

To solve this equation, water penetration and swelling of the hydrophilic matrix, three-dimensional and concentration-dependent diffusion of drug and water, and polymer dissolution are all taken into account simultaneously. The model predicts the in vitro release profile of caffeine from polyethylene oxide (PEO) cylindrical tablets very well. This model also predicts that the polymer dissolution

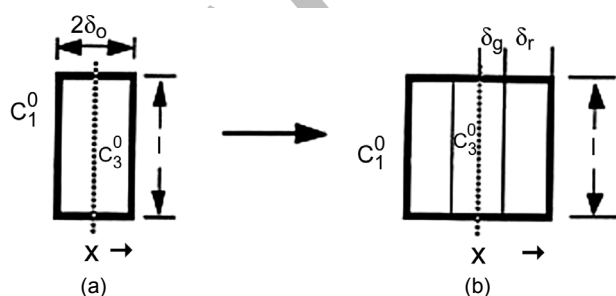


Figure 4. Schematic of swelling-controlled release problem (a thin slab). The initially dry sample (a) undergoes swelling from the lateral surfaces, leading to glassy and rubbery regions separated by a sharp front (b). Adopted from ref [94].

effect on release profile increased while the initial drug loading increases.

Applying the same analysis, Abassi et al. developed a similar mathematical model for caffeine release from a cylindrical cross-linked gelatin or gelatin-maltodextrin hydrogel [98]. The predicted caffeine release profiles are in very good agreement with experimental data at different gel compositions. Consequently, this model could be used for a wide range of bioactive agents and polymeric networks hydrogels with different cylindrical dimensions.

Considering water-induced swelling, drug dissolution, and external and internal mass transport resistances of dissolved drug in an HPMC matrix, Kiil et al. have developed a detailed mathematical model [99]. Estimation of the position of the three distinct moving fronts was the main purpose of their model (Figure 5).

The kinetic equation used to describe the rate of movement of the swelling front (r_s), erosion front (r_E) and diffusion front (r_D), and their initial conditions are as follows [99]:

$$\frac{dr_s}{dt} = -k_s (C_{w2}|_{rs} - C_w^*)^n \dots \dots \dots r_s|_{t=0} = r_0 \quad (43)$$

$$r_E = \sqrt{r_s^2 + (r_0^2 - r_s^2)} f_s \dots \dots \dots r_E|_{t=0} = r_0 \quad (44)$$

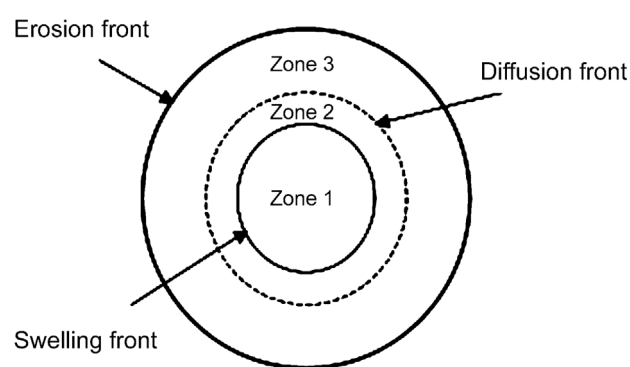


Figure 5. Schematic illustration of a swellable tablet during radial drug release. The dissolved drug profile extends from the diffusion to the erosion front and the water profile from the swelling to the erosion front. Adopted from ref [99].

$$\frac{dr_D}{dt} = \frac{M_D D_{GD} f_s}{V_D \rho_D (1 - \varepsilon_0)} \frac{\partial C_D}{\partial r} \Big|_{r_D} - (f_s - 1) \frac{r_s}{r_D} \frac{dr_s}{dt} \dots\dots\dots$$

$$\dots\dots\dots r_d \Big|_{t=0} = r_0 \quad (45)$$

Here, k_s is the swelling rate constant in the power-law equation for the swelling front and f_s is the expansion factor of the swelling HPMC matrix. C_{w2} is the water concentration in zone 2, C_w^* is the threshold water concentration for swelling and ε_0 is the initial porosity of matrix. D_{GD} is the diffusivity of drug in gel layer, V_D is the initial solid volume fraction of drug and M_D , ρ_D and C_D are the molar mass, density and concentration of drug, respectively. Defining appropriate equations for water and dissolved drug mass balance, change in boundary conditions and cumulative fractional drug release, this model was solved by the method of orthogonal collocation [100]. The model can predict the radial front movements, transient drug fluxes and cumulative fractional drug release behaviours very well. Experimental data cover observations of the swelling, diffusion and erosion front positions over 35 h.

The effect of dynamic loading on solute transport in a gel or cartilage tissue is analyzed theoretically by Mauck et al. [101]. A dynamic load was applied on a cylindrical gel sample, which is placed in a bathing solution containing an excess of neutral solute. The theory of incompressible mixtures and two fluid phases were used to model the gel as a solid matrix and solve the problem of solute transport through its lateral surfaces. Each of the components in this analysis is considered to be of neutral valence and equations solved just for one solute. Mauck et al. showed that under ideal conditions solute diffusivity in the gel is directly proportional to the solvent volumetric fraction [96]. Moreover, they showed that applying a continuous dynamic loading at 1 Hz over a period of approximately three hours could enhance the transport of large solutes, such as growth factors, into the gels and tissues.

Injectable drug delivery devices, which undergo rapid phase inversion on injection, have gained

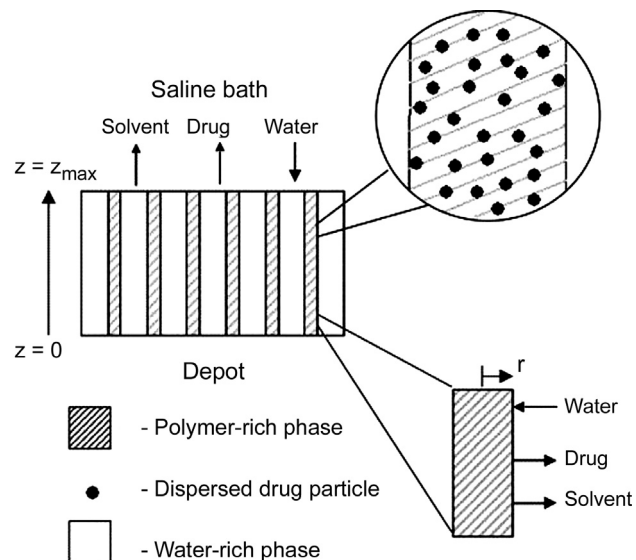


Figure 6. Schematic of the depot release model. Adopted from ref [102].

considerable attention in recent years. Such systems consist of a biodegradable polymer dissolved in a biocompatible solvent, which injected by syringe into the targeted organism. Upon injection, the hydrophobic solution undergoes phase inversion, forming a gel implant. Considering a polymer-rich phase and a solvent-rich phase for these injectable polymeric depots, Raman et al. have developed a mathematical model describing protein release kinetics from such system (Figure 6) [102]. The polymer-rich phase consists of polymer, solvent, dissolved drug and spherical dispersed drug particles. The interconnected water-rich phases contain water, solvent and dissolved drug. When water enters the polymer rich phase, it dissolves dispersed drug particles. The dissolved drug and hydrophobic solvent diffuse radially throughout the polymer-rich phase to the water-rich phase, and then diffuse out axially into the medium. Considering polar coordinates and applying diffusion-reaction mass balances for each species, they obtained two sets of coupled equations, for the polymer-rich and water-rich phases. In the water-rich phase the diffusion-reaction type equations are applied.

In the polymer-rich phase, transport parameters are coupled to the ternary thermodynamics through friction formalism, defining two free parameters: ε as the volume fraction of water-rich phase and k , as

the mass-transfer coefficient for both-side transfer of the protein. They showed that release profiles of proteins will vary from a rapid, burst-like behaviour to a uniform, zero order profile based on the variations of those parameters. Model predictions showed good agreement with experimental data on lysozyme release from PLA, PLGA and PLGA/Pluronic solutions in NMP [102].

Thermally induced swelling-shrinking polymeric membranes have gained considerable attention as on-off drug delivery devices. Interest in this subject started by Heskins and Guillet report on the temperature sensitive properties of poly (*N*-isopropylacrylamide) solution [103]. For the first time, in 1986 Hoffman et al. [104] have shown that such hydrogels may be used to absorb and/or release a variety of biologically and industrially important substances. Bae et al. have studied the on-off thermo-control of solute transport through a NIPAAm network modified with hydrophobic components [105]. Yoshida et al. [106] have developed a zero-order drug release model for poly(*N*-isopropylacrylamide-*co*-alkyl methacrylate) matrixes. Ilman et al. have studied the volume phase transition in an interpenetrating polymer network of poly(acrylamide) and poly(acrylic acid) [107]. Based on their theory, the volume transition in these copolymers is dominated by polymer-water and polymer-polymer that result from hydrogen bonding. Recently, the solute transport across a temperature-sensitive copolymer membrane of DMAEMA and AAm has been studied mathematically by Grassi et al. [108]. They first solved the mass balance equation for the water entering/exiting network, and then, applying the water concentration profile inside the matrix, the drug mass balance has been solved. Considering the Fickian and relaxation contribution to the whole water flux, as well as the relaxation time of the copolymer/water system, D_f and D_r were defined as the diffusion coefficient relative to the Fickian flux and the non-Fickian flux, respectively. Figure 7 shows the relatively good agreement between the mathematical model and the experimental data obtained from the hydrocortisone permeation across a copolymer membrane undergoing stepwise temperature changes. While the medium temperature was kept constant (0-80 min), no swelling/deswelling

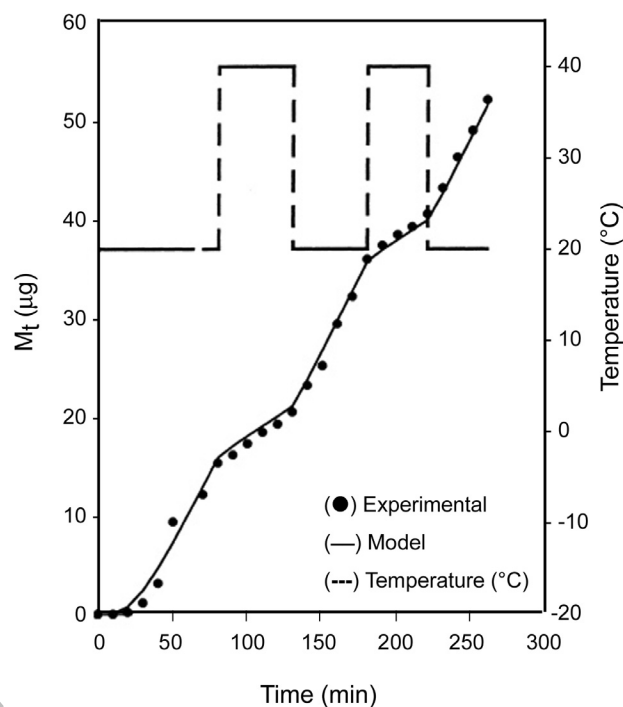


Figure 7. Model fitting of the hydrocortisone permeation through a copolymer II gel undergoing step temperature variations. The permeated amount, M_t , is plotted as a function of time, t . The dashed line indicates the temperature profile [108].

phenomena was observed in the polymeric network. In this period, the cumulative permeated drug amount increased linearly against time. Changing the environmental temperature will change the slope of drug release profile, while maintaining its linear outline. This could be attributed to the huge "drug permeation time" compared with the "swelling/deswelling time" [108].

CONCLUSION

Recently, many hydrogel-based networks have been designed and fabricated to meet the needs of industrial, pharmaceutical and medical fields. The favourable property of these hydrogels is their ability to swell, when put in contact with an aqueous solution. The water attacks the hydrogel surface and penetrates into the polymeric network. Regularly, the meshes of the network in the rubbery phase will start expanding, allowing other solvent molecules to

penetrate within the hydrogel network. Therefore, the unsolvated glassy phase is separated from rubbery hydrogel region with a moving front.

One of the very important features of hydrogel swelling is the rate of swelling or swelling kinetics. It is determined by several physicochemical factors particularly the sample/particle size, porosity extent and the type of the porous structure. In this relation, hydrogels may be divided into four main classes; non-porous, micro-porous, macro-porous and super-porous hydrogels. Non-porous gels have molecular size pores equal to the macromolecular correlation length (10-100 Å), while micro-porous (100-1000 Å) and macro-porous (0.1-1 µm) hydrogels have larger pores. The size of pores in super-porous hydrogels (SPHs) is usually in the range of several hundred micrometers, which are connected to form the open channel system and act as a capillary system causing a rapid uptake of water into the porous structure. Thereby, SPHs swell in aqueous solution to equilibrium state in a matter of a minute regardless of their size.

Osmotic pressure forces, electrostatic forces and viscoelastic restoring forces are the three main forces governing the swelling behaviour of hydrogels. To describe the effect of these different forces adequately, the modelling is conducted on different scales, based on global macroscopic to microscopic theories. The statistical theory, the general theory of porous media, chemo-electro-mechanical multi-field formulation and the discrete element theory are the most famous theories developed during past decades. Kinetics of hydrogel swelling and thermodynamics of equilibrium swelling of hydrogels are the two important topics in these model derivatives. The equilibrium models have been developed to predict the degree of swelling of hydrogels at a given condition. The theoretical description of the swelling of the hydrogels at equilibrium is based on the minimization of Gibbs free energy of the gel. The kinetic models have been developed to predict the rate and mechanism of hydrogel swelling, which are entirely different above and below the glass transition temperature, T_g . The Fickian diffusion models, the collective diffusion models and sigmoidal swelling curves are the famous mathematical models proposed to describe the kinetics of hydrogel

swelling.

The mathematical models and simulations of drug release from swelling-controlled network have also been developed with different approaches and concepts. The choice of an appropriate mathematical model for a specific drug delivery system depends on the chemical reactions and mass transfer processes, which are affected by polymer and drug nature, hydrogel size, shape, composition and encapsulation techniques. Precise description of hydrogel behaviour as well as mathematical description of equilibrium swelling, dimensional changes and drug release profiles will guarantee the successful design of a drug delivery system.

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