Chapter 1

Introductory Chapter: An Overview of Hydrogels

Sutapa Biswas Majee

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/64302

Hydrogels are hydrophilic, water-insoluble polymeric macromolecules represented as semi-open network systems comprising of entangled chains or short strands of varying lengths joined together by cross-links. On being exposed in a thermodynamically compatible solvent (water or any biological fluid), they can entrap a large fraction of solvent within the pores or interstitial spaces and can achieve a fully swollen state. Swelling is accompanied by dimensional change, which leads to a drastic change in the rheological characteristics and ultimately phase transition [1]. These molecules of natural or synthetic origin are endowed with intrinsic physicochemical characteristics such as hydrophilicity, swellability, gelation, mechanical strength, porosity, biocompatibility and biodegradability conferring on them the capability of being utilized in different industries in the area of water purification, ion exchange chromatography, enhanced oil recovery, sensor development, removal of azo-dye pollutants or toxic materials, development of immobilized enzyme systems, agriculture, food processing, pharmaceutical, medical and biomedical fields [2, 3]. Stiffness and water-absorbing capacity of hydrogels are attributed to the presence of hydrophilic pendant moieties attached to the backbone such as alcohols, carboxylic acids and amides, whereas the presence of cross-links makes it resistant to dissolution in the aqueous medium [1]. Some of the common examples of hydrogels include agarose, alginate, chitosan, collagen, fibrin, gelatin, hyaluronic acid, poly(vinyl alcohol), poly(acrylic acid), poly(acrylamide), poly(propylene fumarate-co-ethylene glycol), poly-2-hydroxyethyl methacrylate (PHEMA), polypeptides, etc. [2, 4].

The science of hydrogels is incomplete without a discussion on mathematical models and equations describing swelling thermodynamics and swelling kinetics. Swelling involves the sorption of solvent molecules into the pores or voids in the macromolecular structure of hydrogel. Therefore, porosity constitutes an essential physicochemical parameter, on the basis of which hydrogels may be classified as non-porous, microporous, macroporous and superporous [2, 5]. During hydrogel swelling, two forces come into play: osmotic force and a counter-elastic force, which resists the elongation of macromolecular chains and thus solvent-

induced deformation. Florey and Rehner's equilibrium swelling theory proposed in 1943 laid the foundation stone for mathematical description of the swelling process of polymer networks. Equilibrium or steady state is attained when the counteracting forces of osmotic force and elastic force balance each other and no further swelling occurs and maximum dimensional change has taken place [5, 6]. Several attempts have been made to establish a correlation between network structure of polymeric hydrogel, swelling behaviour and desirable mechanical characteristics, gelation properties and drug-release profile [7].

During adsorption process of metal ions by the non-porous or porous hydrogels, three processes are assumed to occur in succession according to intra-particle diffusion model as proposed by Weber and Morris. They can be described as external mass transfer of the adsorbate on the surface of the adsorbent (film diffusion), internal mass transfer (intraparticle diffusion) of the adsorbate into the pores and capillaries of the adsorbent and chemical-binding reactions. Any of the above-mentioned steps can be the rate-limiting step [8, 9]. Kinetics of adsorption by most of the hydrogels has been successfully described by Freundlich's, Temkin's and Dubinin-Radushkevich's isotherms [10].

Molecular constitution of the hydrogels affects their in vitro and in vivo performance during any conceivable application of hydrogel in any sphere of life. Chemical or physical cross-linking produces irreversible or reversible gels, respectively, with improved spatial and temporal control of cross-linking, thereby producing gels of tunable mechanical strength, elasticity, gelation characteristic and in vivo degradation/erosion rate [1, 11]. Introduction of different substituent groups or chemical cross-links between identical/different monomers or similar/dissimilar polymers involves the formation of permanent covalent bonds, induces configurational changes and imparts greater stability than physical gels held together by ionic bonds, hydrogen bonds or hydrophobic forces and chain entanglements. Conformational changes are manifested in physical gels. For cross-linking, chemicals such as carbodiimides, formaldehyde and glutaraldehyde have been frequently used. Different reactions involved in producing chemically cross-linked hydrogels include free radical polymerization, addition and condensation polymerization, classical organic reactions between functional groups (viz. Michael addition, click reaction, Schiff base formation, epoxide coupling, etc.), enzymatic reactions and gamma and electron beam polymerization as well as grafting. Polymerization can be carried out in solution, suspension or emulsion phase [2, 12]. Gelatin matrix has been cross-linked with oxidized cellulose nanowhiskers for enhanced mechanical strength and better thermal stability [13–15]. The parameters that control the micro-architecture and hydrogel attributes include the concentration of the cross-linking agent, structure and concentration of the monomers [1, 11]. It is much easier to initiate disintegration of physical or reversible gels through alteration of adjacent environmental parameters such as pH, temperature, solvent composition, ionic strength and electric field. Physical hydrogels, which are capable of responding to changes in the above-mentioned internal or external stimuli, are termed as 'smart' or 'intelligent' polymers. Swelling and volume phase transition of these 'smart' polymers may be either continuous or discontinuous over a range of level of stimulus or at a threshold level of the stimulus. Since, synthetic hydrogels usually contain ionic or ionizable groups, they are known as polyelectrolyte gels and are reported to possess higher

swelling capacity than the nonionic gels[1]. For these gels, interaction with mobile counterions in the medium has an effect on the hydrogel behaviour and performance. High cross-link density in polyelectrolyte gels may not lead to spatial inhomogeneity or network imperfections as in the case of nonionic gels [1, 3, 4]. At this juncture, it is worth mentioning that the change in environmental pH does not act as a stimulus for nonionic gels [4].

Various instrumental techniques such as dynamic contact angle analysis, tensile analysis and thermogravimetry are employed to study surface topography, mechanical properties and swelling behaviour. Mechanical properties of a hydrogel are time-dependent where poroelasticity is attributed to solvent imbibition and its movement whereas viscoelasticity results from the rearrangement of polymer chains bound together by reversible and irreversible cross-links. Mechanical characterization of hydrogels through extensiometry, parallel plate compression test, bulge test and indentation test provides a precise idea about gel parameters such as Young's modulus, yield strength, tensile strength, viscoelastic and poroelastic properties [16, 17]. Rheological behaviour is analysed with the help of oscillatory shear rheometry through dynamic frequency sweep tests [18]. Modulated differential scanning calorimetry (DSC) is utilized in the characterization of temperature-dependent changes in hydrogel properties [4]. Hydrogels with specific ligands or chelating agents attached to the polymeric backbone are known to adsorb or absorb metal ions or organic compounds such as fertilizers and can be used to either remove heavy metal ions from a particular system or release the encapsulated phosphorous-containing fertilizers slowly over a prolonged time period, thereby facilitating plant nutrition. The adsorbed/absorbed components and state of metal ion coordination can be studied by different spectroscopic techniques. Spectroscopic methods, if properly utilized, can provide valuable information on the micro-architecture and interactions occurring between polymer and water, mesh-size distribution and also about the phenomena of solvent diffusion and release of the embedded/entrapped molecules [19–21].

For biomedical applications in the area of regenerative medicine, tissue adhesion and design of three-dimensional (3D) tissue engineering scaffolds for cellular growth, an ideal hydrogel should possess excellent biocompatibility, low immunogenicity, capability of integrating and encoding biologically active motifs or functional groups in the network structure, in addition to optimum network architecture, porosity and desirable mechanical properties and stiffness to promote cell-cell interactions, cell-polymer bioadhesion, cellular penetration, proliferation, differentiation and migration [11, 14]. In situ-forming hydrogels are gaining popularity among scientists engaged in biomedical research. Extreme precaution should be taken during selection of monomers, cross-linking agent, initiator and catalyst as well as the reaction conditions should be highly specific in order to minimize cytotoxicity and immunogenicity. The formation of hydrogel in the presence of specific ions, inclusion complexes with β-cyclodextrin, stereocomplexation and complementary-binding reactions are some of the methods to produce in situ-forming hydrogels [22]. The ultimate objective of hydrogel-based tissue constructs is to mimic native tissue and extracellular matrix as closely as possible, that is, they should be bio-mimetic. Moreover, the hydrogel should retain its integrity after administration by parenteral routes and encapsulated cells should maintain their viability and phenotype. Natural polymer gelatin possesses Arg-Gly-Asp (RGD) sequences, which act as

sites for adhesion to cell surfaces through integrins [13]. However, native gelatin fails to perform efficiently as scaffold material owing to its low mechanical strength and shape stability at body temperature. Therefore, numerous studies have been carried out to produce cross-linked gelatin for the development of engineered tissues such as cartilage, bone and smooth muscle [3, 13, 15]. Another study reported the effect of elastic and viscous modulus of modified alginate hydrogels on the rate of proliferation and differentiation of embedded neural stem cells. The modulus value of the alginate gel is controlled by the molecular weight distribution of the polymer, divalent ion concentration and the α-L-guluronic acid content in the gel [18, 23]. Recently, different three-dimensional bioprinting techniques are being exploited to design hydrogel-based bio-scaffolds for hard and soft tissues containing viable cells [24]. Self-healing hydrogels are gaining popularity because of their unique capability of autonomous healing and repair on damage. They can be either linear polymers or supramolecular networks, and recent advances have been made in inducing self-healing property in hydrogels with permanent cross-links [25].

Alterations in the degree and density of cross-linking of the hydrogels and hydrogels with different hydrophilicity/hydrophobicity ratios have enabled the development of drug-delivery devices with tailor-made and preprogrammed release profiles. Different hydrogels thus obtained show different solubilities in aqueous medium and also characteristic swelling behaviour. Among the synthetic polymers commercially available, hydroxypropylmethyl cellulose (HPMC) is the most commonly used polymer in the development of different dosage forms because of its availability in different grades varying in their degree and type of substitution, cross-linking density, sensitivity to pH and temperature, rheological and swelling behaviour as well as drug-release profiles [4]. Drug entrapment and its subsequent release from hydrogels are governed by porosity and degradability of the gels. Solvent influx or absorption and drug release from the hydrogel matrices or reservoirs occurs primarily by the process of diffusion, although swelling and erosion/biodegradation may also contribute to the release phenomenon depending upon the chemical structure of the hydrogel [3, 6, 23]. The devices may exhibit Fickian or non-Fickian diffusion kinetics. Although diffusion is the primary mechanism for solvent influx and efflux of entrapped molecules, convection may play a significant role in the transport of water molecules into or drug molecules or out of the hydrogel matrix [6]. Hydrogels have shown great promise in metal-based therapy as intelligent carriers for anticancer drugs like cisplatin where a complex of well-defined stoichiometry resulted and the encapsulated platinum was released obeying near zero-order kinetics demonstrating remarkable cytotoxic activity [26]. Similar cytotoxic effect has also been observed with herceptin loaded into hydrogel exhibiting improved therapeutic efficacy and better retention inside the tumour [27].

By virtue of their unique property of being stimuli-responsive, thermo-sensitive hydrogels have found wide spectrum of applications in the field of parenteral drug delivery since they can undergo gelation or sol-gel transformation readily at body temperature, especially at sites of Inflammation having elevated temperature [28]. Thermoresponsive hydrogels exhibit a lower critical solution temperature (LCST) where there is a sudden change in aqueous solubility and gelation characteristics of hydrogels and this is often termed as volume-phase

transition temperature (VPTT). Swelling occurs below LCST and gel network collapses due to dehydration above the critical temperature. Temperature-induced volume-phase transition behaviour is thus governed by water-polymer interactions [4, 29, 30]. Temperature sensitivity of hydrogels has also been exhibited by hydrophobically modified hydrogels where a phenomenon known as re-entrant swelling transition along with change in size is manifested in aqueous solution of non-polar solvents as observed in the case of poly(N-isopropyl acrylamide) (PNIPAAm) [1]. Linear copolymer of PNIPAAm and N-hydroxymethylacrylamide (HMAAm) has been synthesized as cross-linked thermoresponsive polymer and investigated as microparticulate carrier for drug molecules. Drug diffusion through the matrix of the microspheres depended highly on the presence of salt in the medium and its temperature. Above VPTT, the collapse of the gel network, exposure of the hydrophobic domains and subsequent shrinkage retarded drug release although some of the dissolved drug is mechanically expelled out. Below VPTT, diffusion was faster ultimately leading to pulsatile drug release from cross-linked copolymer microspheres over the temperature range studied [4, 29].

Physical hydrogels exhibiting shear-thinning and self-healing properties during and after injection respectively can be exploited for controlled and minimally invasive delivery of biologically active molecules, proteins and peptides in the form of injectable delivery systems. They show lower viscosity or fluidity on the application of shear stress rendering syringeability, which is recovered on relaxation at the site of application, when shear is absent. Therefore, these systems exhibit shear-dependent sol-gel transformation. The desirable qualities of an injectable drug delivery system include customized mechanical strength, stability, biodegradation rate, erosion in addition to minimum toxicity and maximum biocompatibility [31]. Hydrogels have also gained attention in the field of topical and transdermal drug delivery as also in ocular drug delivery and in the manufacture of different types of contact lenses differing in their flexibility, water vapour transmission and gas permeability. Fabrication of gastroretentive dosage forms for oral administration through the use of superporous hydrogels has offered new possibilities in achieving sustained drug release [3].

Constant efforts are being made to improve mechanical properties of hydrogels and also to obtain fast response to various exogenous stimuli. Topological gels, double-network gels or interpenetrating network consisting of two polymeric entities with different degree of stiffness, nanocomposite gels containing PNIPAAm and inorganic clay, tetrapoly(ethylene glycol) gels submicrometer-sized gel particles, gels having dangling chains and macroporous gels have been designed with this objective [1, 32]. In biomedical field, hydrogels can be employed in controlling the process of vascularization through controlled release of vascular endothelial growth factor (VEGF) and other angiogenic factors at the desired target site. However, hydrogel-based tissue scaffolds are yet to be commercially viable because of the huge expenditure involved [23, 33].

Therefore, modifications in the chemistry and architecture of hydrogels and advances in the field of 'smart' or stimuli-responsive hydrogels and self-healing hydrogels have opened up new avenues in the fabrication of bio-mimetic scaffolds, artificial tissues and organs, drug delivery systems, injectable hydrogels and controlled release systems for fertilizers. Physicochemical characterization of hydrogel parameters, mathematical modelling of polymer-

solvent interaction during hydrogel swelling and sorption phenomena will enable in the future evolution of hydrogel materials.

Author details

Sutapa Biswas Majee

Address all correspondence to: sutapabiswas2001@yahoo.co.in

Division of Pharmaceutics, NSHM College of Pharmaceutical Technology, NSHM Knowledge Campus, Kolkata Group of Institutions, Kolkata, West Bengal, India

References

[1] Okay O (2009). General properties of hydrogels. *In* Hydrogel sensors and actuators. G. Gerlach and K.F. Arndt (eds.). Springer Series on Chemical Sensors and Biosensors, 6, Springer–Verlag Berlin Heidelberg. (http://www.springer.com/978-3-540-75644-6).

[2] Ahmed EM (2015). Hydrogel: Preparation, characterization, and applications: A review. *Journal of Advanced Research* 6, 105–121.

[3] Calo E and Khutoryanskiy VV (2015). Biomedical applications of hydrogels: A review of patents and commercial products. *European Polymer Journal* 65, 252–267.

[4] Omidian H and Park K (2012). Hydrogels. *In* Fundamentals and applications of controlled release drug delivery, J.Siepmann, R. Siegel and M. Rathbone (eds.). Controlled Release Society, Springer New York, 75–106 (DOI: 10.1007/978-1-4614-0881-9).

[5] Ganji F, Vasheghani-Farahani S and Vasheghani-Farahani E (2010). Theoretical description of hydrogel swelling: A review. *Iranian Polymer Journal* 19, 375–398.

[6] Porter TL, Stewart R, Reed J and Morton K (2007). Models of hydrogel swelling with applications to hydration sensing. *Sensors* 7,1980–1991.

[7] Brannon-Peppas L and Peppas NA (1991). Equilibrium swelling behavior of pH-sensitive hydrogels. *Chemical Engineering Science* 46, 715–722.

[8] Chen Y, Zhang Q, Chen L , Bai H and Li L (2013). Basic aluminum sulfate@graphene hydrogel composites: Preparation and application for removal of fluoride. *Journal of Materials Chemistry A* 1, 13101–13110.

[9] Medina RP, Ballesteros FC and Rodrigues DF (2015). The influence of physical configuration on the performance of chitosan–poly(acrylic acid) hydrogel beads as adsorbent

for lead(II). *Proceedings of the 14th International Conference on Environmental Science and Technology*, Rhodes, Greece.

[10] Saeed R and Ul Abdeen Z (2014). Sorption and kinetics study of potassium chloride in polyvinyl alcohol-borate hydrogel. *International Journal of Scientific and Technology Research* 3, 321–327.

[11] Zhang YN, Avery RK, Vallmajo-Martin Q, Assmann A, Vegh A, Memic A, Olsen BD, Annabi N and Khademhosseini A (2015). A highly elastic and rapidly crosslinkable elastin-like polypeptide-based hydrogel for biomedical applications. *Advanced Functional Materials* 25, 4814–4826.

[12] Maitra J and Shukla VK (2014). Cross-linking in hydrogels—A review. *American Journal of Polymer Science* 4, 25–31.

[13] Xing Q, Yates K, Vogt C, Qian Z, Frost MC and Zhao F (2014). Increasing mechanical strength of gelatin hydrogels by divalent metal ion removal. *Scientific Reports* 4, 4706.

[14] Yue K, Trujillo-de Santiago G, Moises Alvarez M, Tamayol A, Annabi N and Khademhosseini A (2015). Synthesis, properties, and biomedical applications of gelatin methacryloyl (GelMA) hydrogels. *Biomaterials* 73, 254–271.

[15] Cao L, Cao B, Lu C, Wang G, Yu L and Ding J (2015). An injectable hydrogel formed by *in situ* cross-linking of glycol chitosan and multi-benzaldehyde functionalized PEG analogues for cartilage tissue engineering. *Journal of Materials Chemistry B* 3, 1268–1280.

[16] Ahearne M, Yang Y and Liu KK (2008). Mechanical characterisation of hydrogels for tissue engineering applications. *In* Topics in tissue engineering, Vol. 4. N. Ashammakhi, R Reis and F Chiellini (eds.).Available from : http://www.oulu.fi/spareparts/ebook-topics-in-t-e-vol4/published-chapters.html.

[17] Wang QM, Mohan AC, Oyen ML and Zhao XH (2014). Separating viscoelasticity and poroelasticity of gels with different length and time scales. *Acta Mechanica Sinica* 30, 20–27.

[18] Banerjee A, Arha M, Choudhary S, Ashton RS, Bhatia SR, Schaffer DV and Kane RS (2009). The influence of hydrogel modulus on the proliferation and differentiation of encapsulated neural stem cells. *Biomaterials* 30, 4695–4699.

[19] Wallace M, Adams DJ and Iggo JA (2013). Analysis of the mesh size in a supramolecular hydrogel by PFG-NMR spectroscopy. *Soft Matter* 9, 5483–5491.

[20] Bäckström S, Benavente J, Berg RW, Stibius K, Larsen MS, Bohr H and Hélix-Nielsen C (2012). Tailoring properties of biocompatible PEG-DMA hydrogels with UV light. *Materials Science Applications* 3, 425–431.

[21] Ferro M, Castiglione F , Punta C, Melone L, Panzeri W, Rossi B, Trotta F and Mele A(2014). Anomalous diffusion of ibuprofen in cyclodextrin nanosponge hydrogels: An HRMAS NMR study. *Beilstein Journal of Organic Chemistry* 10, 2715–2723.

[22] Choi B, Loh XJ, Tan A, Loh CK, Ye E, Joo MK and Jeong B (2015). Introduction to in situ forming hydrogels for biomedical applications. *In* In-situ gelling polymers, Series in BioEngineering X.J. Loh (ed.) Springer Science+Business Media.(http://www.springer.com/978-981-287-151-0).

[23] Silva EA and Mooney DJ (2007). Spatiotemporal control of vascular endothelial growth factor delivery from injectable hydrogels enhances angiogenesis. *Journal of Thrombosis and Haemostasis* 5, 590–598.

[24] Tabriz AG, Hermida MA, Leslie NR and Shu W (2015). Three-dimensional bioprinting of complex cell laden alginate hydrogel structures. *Biofabrication* 7, 045012.

[25] Phadke A, Zhang C, Arman B, Hsu CC, Mashelkar RA, Lele AK, Tauber MJ, Arya G and Varghese S (2012). Rapid self-healing hydrogels. *PNAS*,109, 4383–4388.

[26] Casolaro M, Cini R, Del Bello B, Ferrali M and Maellaro E (2009). Cisplatin/hydrogel complex in cancer therapy. *Biomacromolecules* 10, 944–949.

[27] Lee ALZ, Ng VWL, Gao S, Hedrick JL and Yang YY (2014). Injectable hydrogels from triblock copolymers of vitamin e-functionalized polycarbonate and poly(ethylene glycol) for subcutaneous delivery of antibodies for cancer therapy. *Advanced Functional Materials* 24, 1538–1550.

[28] Sinha MK, Gao J, Stowell CET and Wang Y (2015). Synthesis and biocompatibility of a biodegradable and functionalizable thermo-sensitive hydrogel. *Regenerative Biomaterials* 2, 177–85.

[29] Constantin M, Cristea M, Ascenzi P, Fundueanu G (2011). Lower critical solution temperature versus volume phase transition temperature in thermoresponsive drug delivery systems. *eXPRESS Polymer Letters* 5, 839–848.

[30] Mah E and Ghosh R (2013). Thermo-responsive hydrogels for stimuli-responsive membranes. *Processes* 1, 238–262.

[31] Guvendiren M, Lu HD and Burdick JA (2012). Shear-thinning hydrogels for biomedical applications. *Soft Matter* 8, 260–272.

[32] Noda Y, Hayashi Y and Ito K (2014). From topological gels to slide-ring materials. *Journal of Applied Polymer Science.* 131, 40509–517

[33] Corbin EA, Millet LJ, Pikul JH, Johnson CL, Georgiadis JG, King WP and Bashir (2013). Micromechanical properties of hydrogels measured with MEMS resonant sensors. *Biomedical Microdevices*. 15, 311–19.